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     (FILE 'HOME' ENTERED AT 11:11:55 ON 09 SEP 2002)

     FILE 'HCAPLUS' ENTERED AT 11:12:06 ON 09 SEP 2002
L1            21 S PACCIARINI M?/AU
L2             8 S VALOTA O?/AU
L3           644 S KERR D?/AU
L4           671 S L1-3
L5            38 S L4 AND LIVER
L6             1 S L5 AND ANTHRACYC?
                 SELECT RN L6 1

     FILE 'REGISTRY' ENTERED AT 11:13:28 ON 09 SEP 2002
L7             1 S E1

     FILE 'HCAPLUS' ENTERED AT 11:14:12 ON 09 SEP 2002
L8             1 S L6 AND L7
L9            53 S L7
L10           52 S L9 NOT L8
L11           13 S L10 AND ?LIVER?
L12      1021213 S BOLOS OR IV OR IODIZ?(5A)OIL OR INFUS? OR INTRAVEN? OR HEPATI
L13           12 S L11 AND L12
L14          207 S IODIZ?(5A)OIL
L15           33 S L14 AND LIVER
L16        15594 S BOLUS
L17            1 S L16 AND L11
L18            0 S L17 NOT L13
L19      1113893 S BOLUS OR IV OR INFUS? OR INTRAVEN? OR ?HEPATIC OR HEPATIC ART
L20           21 S L15 AND L19
L21           39 S L10 NOT L11
L22           34 S L21 NOT PATENT/DT
L23           32 S L22 AND PD<19990827
L24           30 S L7/THU
L25           17 S L24 AND L23
L26            5 S L21 AND PATENT/DT
L27            1 S L26 AND L24
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inventor search

claimed cpd

1 citation w/ one cpd shown

53 cites for claimed cpd

12 cites related to "liver"

correction for misspelling in L12 (BOLOS)

21 cites for use of iodized oil in a medical way (for 103)

remaining cites from L10

therapeutic role

17 journal articles

1 patent

not related to liver

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L8 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:190906 HCAPLUS
DOCUMENT NUMBER: 132:231945
TITLE: Intrahepatic administration of methoxymorpholinodoxorubicin for the treatment of a **liver** tumor
INVENTOR(S): **Pacciarini, Maria Adele; Valota, Olga; Kerr, David**
PATENT ASSIGNEE(S): Pharmacia & Upjohn S.P.A., Italy
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000015203	A2	20000323	WO 1999-EP6298	19990827
WO 2000015203	A3	20000720		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9957421	A1	20000403	AU 1999-57421	19990827
BR 9913627	A	20010522	BR 1999-13627	19990827
EP 1112066	A2	20010704	EP 1999-944533	19990827
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002524496	T2	20020806	JP 2000-569787	19990827
NO 2001001116	A	20010514	NO 2001-1116	20010305

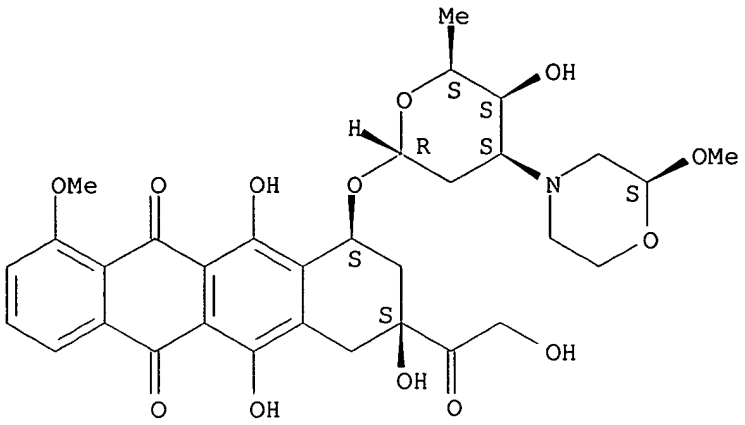
PRIORITY APPLN. INFO.: GB 1998-20012 A 19980914
WO 1999-EP6298 W 19990827

AB The invention discloses the use of methoxymorpholinodoxorubicin for the treatment of a **liver** cancer; in particular, it discloses the intrahepatic administration of methoxymorpholinodoxorubicin for use in the **liver** tumor therapy, optionally in assocn. with an agent, e.g. iodized oil, which remains selectively in the **liver** tumor after its injection through the hepatic artery.

IT **108852-90-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methoxymorpholinodoxorubicin intrahepatic administration for treatment of **liver** tumor)

RN 108852-90-0 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-.alpha.-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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L8 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2002 ACS
IC ICM A61K031-00
CC 1-6 (Pharmacology)
Section cross-reference(s): 63
ST methoxymorpholinodoxorubicin **liver** tumor treatment; iodized oil methoxymorpholinodoxorubicin **liver** tumor treatment; **anthracycline** deriv **liver** tumor treatment
IT Drug delivery systems
(bolus; methoxymorpholinodoxorubicin intrahepatic administration for treatment of **liver** tumor)
IT Biliary tract
Biliary tract
(cholangioma, inhibitors; methoxymorpholinodoxorubicin intrahepatic administration for treatment of **liver** tumor)
IT Antitumor agents
(cholangioma; methoxymorpholinodoxorubicin intrahepatic administration for treatment of **liver** tumor)
IT Artery
(hepatic; methoxymorpholinodoxorubicin intrahepatic administration for treatment of **liver** tumor)
IT **Liver**, neoplasm
Liver, neoplasm
(hepatoma, inhibitors; methoxymorpholinodoxorubicin intrahepatic administration for treatment of **liver** tumor)
IT Antitumor agents
(hepatoma; methoxymorpholinodoxorubicin intrahepatic administration for treatment of **liver** tumor)
IT Drug delivery systems
(infusions; methoxymorpholinodoxorubicin intrahepatic administration for treatment of **liver** tumor)
IT Antitumor agents
(**liver**, metastasis; methoxymorpholinodoxorubicin intrahepatic administration for treatment of **liver** tumor)
IT **Liver**, neoplasm
(metastasis, inhibitors; methoxymorpholinodoxorubicin intrahepatic administration for treatment of **liver** tumor)
IT Drug delivery systems
(methoxymorpholinodoxorubicin intrahepatic administration for treatment of **liver** tumor)

IT Fats and Glyceridic oils, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(poppyseed, iodinated; methoxymorpholinodoxorubicin intrahepatic administration for treatment of **liver** tumor)

IT **108852-90-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methoxymorpholinodoxorubicin intrahepatic administration for treatment of **liver** tumor)

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L13 ANSWER 1 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:521462 HCAPLUS
DOCUMENT NUMBER: 137:88442
TITLE: Incensole and furanogermacrens and compounds in treatment for inhibiting neoplastic lesions and microorganisms
INVENTOR(S): Shanahan-Pendergast, Elisabeth
PATENT ASSIGNEE(S): Ire.
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002053138	A2	20020711	WO 2002-IE200001	20020102

W: AE, AG, AT, AU, BB, BG, CA, CH, CN, CO, CU, CZ, LU, LV, MA, MD, UA, UG, US, VN, YU, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, AT, BE, CH, CY, DE, ES, FI, ML, MR, NE, SN, TD, TG

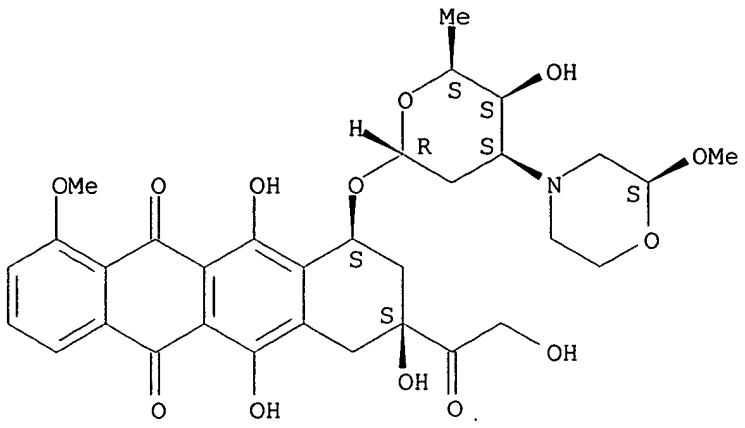
PRIORITY APPLN. INFO.: IE 2001-2 A 20010102
OTHER SOURCE(S): MARPAT 137:88442

AB The invention discloses the use of incensole and/or furanogermacrens, derivs. metabolites and precursors thereof in the treatment of neoplasia, particularly resistant neoplasia and immundysregulatory disorders. These compds. can be administered alone or in combination with conventional chemotherapeutic, antiviral, antiparasite agents, radiation and/or surgery. Incensole and furanogermacren and their mixt. showed **antitumor** activity against various human **carcinomas** and melanomas and antimicrobial activity against Staphylococcus aureus and Enterococcus faecalis.

IT **108852-90-0**, Nemorubicin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical formulation further including; incensole and furanogermacrens and compds. as **antitumor** and antimicrobial agents)

RN 108852-90-0 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-.alpha.-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.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=> d ibib abs hitstr 2

L13 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:275788 HCAPLUS
DOCUMENT NUMBER: 136:304046
TITLE: **Antitumor** therapy comprising distamycin derivatives
INVENTOR(S): Fowst, Camilla; Vreeland, Franzanne; Geroni, Maria Cristina Rosa
PATENT ASSIGNEE(S): Pharmacia & Upjohn S.P.A., Italy; Pharmacia & Upjohn Company
SOURCE: PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002028389	A1	20020411	WO 2001-EP10988	20010921

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

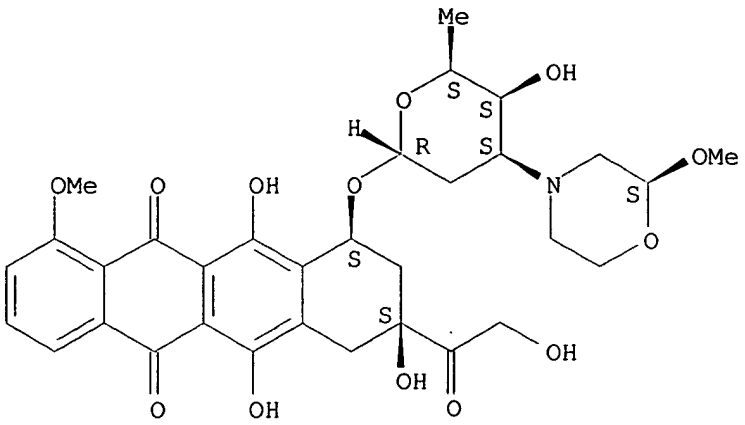
PRIORITY APPLN. INFO.: US 2000-676770 A 20001002
OTHER SOURCE(S): MARPAT 136:304046

AB The present invention relates to an administration schedule comprising the i.v. administration of a .alpha.-halogen-acryloyl distamycin deriv., or a pharmaceutically acceptable salt thereof. The above administration allows the treatment of a variety of **tumors** in mammals. N-[5-[[[5-[[[5-[[[2-[[amino(imino)methyl]amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride was administered by i.v. **infusion** to patients with solid **tumors**.

IT **108852-90-0**, Nemorubicin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in combination with; **antitumor** therapy comprising distamycin derivs.)

RN 108852-90-0 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-.alpha.-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L13 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:184907 HCAPLUS
DOCUMENT NUMBER: 136:241643
TITLE: Exemestane as chemopreventing agent
INVENTOR(S): Di Salle, Enrico; Piscitelli, Gabriella; Massimini, Giorgio; Purandare, Dinesh; Martini, Alessandro; Muggetti, Lorena
PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy; Pharmacia & Upjohn Company
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002020020	A1	20020314	WO 2001-EP10172	20010831
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001089865	A5	20020322	AU 2001-89865	20010831

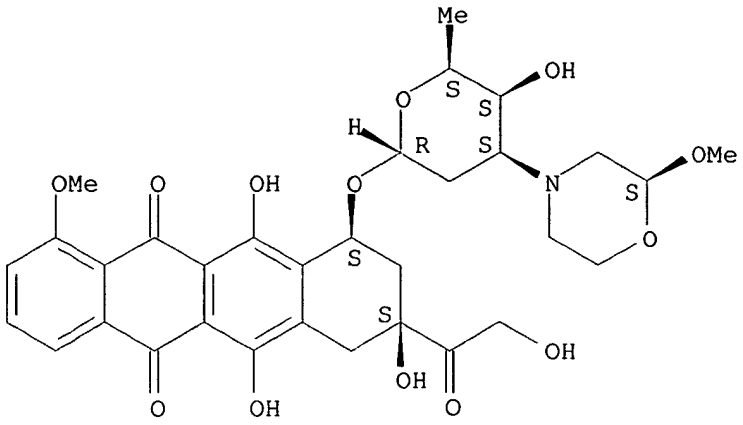
PRIORITY APPLN. INFO.: US 2000-658052 A 20000908
WO 2001-EP10172 W 20010831

AB The present invention concerns the use of aromatase inhibitor exemestane, either alone or in combination with other therapeutic agents, in the chemoprevention of estrogen dependent cancer in mammals, including humans, at increased risk of the disease. Exemestane treatment (4, 20 or 100 mg/kg/wk, IM), started 1 wk after dimethylbenzanthracene (DMBA) exposure (20 mg/rat, PO) and continued for 19 wk, significantly decreased **tumor** incidence from 85 % in vehicle treated rats to 13.6 % in the 100 mg/kg treated group. Moreover, exemestane at 100 mg/kg reduced significantly the **tumor** multiplicity, being 2.55 the no. of **tumors**/rat in the control groups vs. 0.27 in the treated group. No signs of toxicity were obsd.

IT **108852-90-0**, Nemorubicin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in combination; exemestane as chemopreventing agent for estrogen-dependent cancer)

RN 108852-90-0 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-.alpha.-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

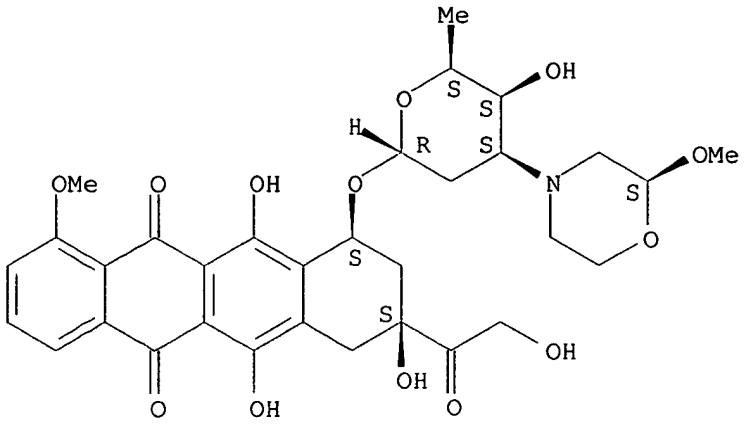
=> d ibib abs hitstr 4

L13 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:126947 HCAPLUS
DOCUMENT NUMBER: 137:27771
TITLE: Metabolism of methoxymorpholino-doxorubicin in rat, dog and monkey **liver** microsomes: comparison with human microsomes
AUTHOR(S): Beulz-Riche, Dominique; Robert, Jacques; Menard, Christophe; Ratanasavanh, Damrong
CORPORATE SOURCE: Service de Pharmacologie et Centre regional de pharmacovigilance, CHU de la Cavale Blanche, Brest, 29609, Fr.
SOURCE: Fundamental & Clinical Pharmacology (2001), 15(6), 373-378
CODEN: FCPHEZ; ISSN: 0767-3981
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The morpholino anthracycline, methoxymorpholino-doxorubicin (MMDx) is a novel anticancer agent. The metab. of this highly lipophilic doxorubicin analog is not fully elucidated. MMDx is metabolically activated in vivo, resulting in an 80-fold increase in potency over the parent drug. In this study, MMDx in vitro metab. was compared in rat, dog, monkey and human **liver** microsomes. When microsomal fractions were incubated with MMDx, 6-8 metabolites were formed depending on the species and on the substrate concns. Among these eight metabolites, three comigrated with authentic stds., namely MMDx-ol, PNU156686 and PNU159682, and the five others are in the process of being characterized. Quant., monkey and human metabolize MMDx with a higher rate than rat and dog. Qual., MMDx metabolic profile in dog microsomes was different from the three other species. MMDx-ol was predominant in dog and only minor in other species. In conclusion, MMDx metab. was species-different. Rat and monkey **liver** microsomes may be used as models to study MMDx metab. in humans. Dog **liver** microsomes may be a good model for studying the formation of MMDx-ol.

IT **108852-90-0**, PNU 152243
RL: BSU (Biological study, unclassified); PKT (Pharmacokinetics); BIOL (Biological study)
(methoxymorpholino-doxorubicin metab. in different species microsomes in comparison with human microsomes)
RN 108852-90-0 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-.alpha.-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 5

L13 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:935387 HCAPLUS
DOCUMENT NUMBER: 136:64105
TITLE: Combined therapy against **tumors** comprising substituted acryloyl distamycin derivatives and topoisomerase I and II inhibitors
INVENTOR(S): Geroni, Maria Cristina Rosa; Cozzi, Paolo; Beria, Italo
PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy
SOURCE: PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001097789	A2	20011227	WO 2001-EP7059	20010620
WO 2001097789	A3	20020516		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2000-15444 A 20000623
OTHER SOURCE(S): MARPAT 136:64105
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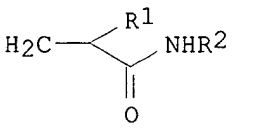


I

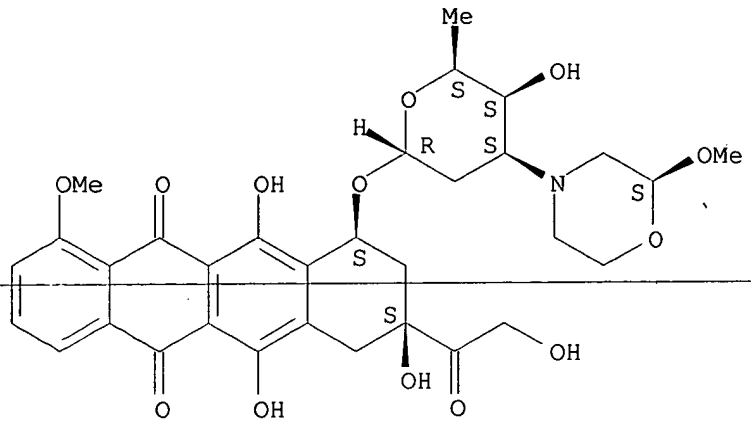
AB The present invention provides the combined use of acryloyl distamycin derivs., in particular .alpha.-bromo- and .alpha.-chloro-acryloyl distamycin derivs. I (R1 = Br, Cl; R2 = distamycin or distamycin-like framework) and an antineoplastic topoisomerase I or II inhibitor, in the treatment of **tumors**. Also provided is the use of the said combinations in the treatment or prevention of **metastasis** or in the treatment of **tumors** by inhibition of angiogenesis. Mice with disseminated L1210 murine leukemia were treated synergistically with N-[5-[[[5-[[[5-[[[2-[[amino(imino)methyl]amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride and doxorubicin.
IT **108852-90-0**, Nemorubicin

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as topoisomerase II inhibitors; combined therapy against **tumors** comprising substituted acryloyl distamycin derivs. and topoisomerase I and II inhibitors)

RN 108852-90-0 HCAPLUS

CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-.alpha.-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> d ibib abs hitstr 6

L13 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:438786 HCAPLUS
DOCUMENT NUMBER: 133:144561
TITLE: In vivo **antitumor** activity and host toxicity of methoxymorpholinyl doxorubicin: role of cytochrome P450 3A
AUTHOR(S): Quintieri, Luigi; Rosato, Antonio; Napoli, Eleonora; Sola, Francesco; Geroni, Cristina; Floreani, Maura; Zanovello, Paola
CORPORATE SOURCE: Oncology Section, Department of Oncology and Surgical Sciences, University of Padova, Padua, 35128, Italy
SOURCE: Cancer Research (2000), 60(12), 3232-3238
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Methoxymorpholinyl doxorubicin (MMDX; PNU 152243) is a promising doxorubicin deriv. currently undergoing clin. evaluation. Previous in vitro studies suggested that the compd. undergoes hepatic biotransformation by cytochrome P 450 (CYP) 3A into a more cytotoxic metabolite(s). The present study examd. the role of CYP3A-mediated metab. in the in vivo **antitumor** activity and host toxicity of MMDX in the mouse model and investigated the potential for increasing the therapeutic effectiveness of the drug by inducing its hepatic CYP-catalyzed activation. We found that MMDX cytotoxicity for cultured M5076 **tumor** cells was potentiated 22-fold by preincubating the drug with NADPH-supplemented **liver** microsomes from untreated C57BL/6 female mice. A greater (50-fold) potentiation of MMDX cytotoxicity was obsd. after its preincubation with **liver** microsomes isolated from animals pretreated with the prototypical CYP3A inducer pregnenolone-16.alpha.-carbonitrile. In contrast, in vivo administration of the selective CYP3A inhibitor troleandomycin (TAO) reduced both potentiation of MMDX cytotoxicity and the rate of CYP3A-catalyzed N-demethylation of erythromycin by isolated **liver** microsomes (55.5 and 49% redn., resp.). In vivo **antitumor** activity expts. revealed that TAO completely suppressed the ability of 90 .mu.g/kg MMDX i.v., a dose close to the LD10, to delay growth of s.c. M5076 **tumors** in C57BL/6 mice and to prolong survival of DBA/2 mice with disseminated L1210 leukemia. Moreover, TAO administration markedly inhibited the therapeutic efficacy of 90 .mu.g/kg MMDX i.v. in mice bearing exptl. M5076 **liver metastases**; a complete loss of MMDX activity was obsd. in **liver metastases** -bearing animals receiving 40 .mu.g/kg MMDX i.v. plus TAO. However, pregnenolone-16.alpha.-carbonitrile pretreatment failed to enhance MMDX activity in mice bearing either s.c. M5076 **tumors** or exptl. M5076 **liver metastases**. Addnl. expts. carried out in healthy C57BL/6 mice showed that TAO markedly inhibited MMDX-induced myelosuppression and protected the animals against LDs of MMDX. Taken together, these findings demonstrate that an active metabolite(s) of MMDX synthesized via CYP3A contributes significantly to its in vivo **antitumor** activity and host toxicity.

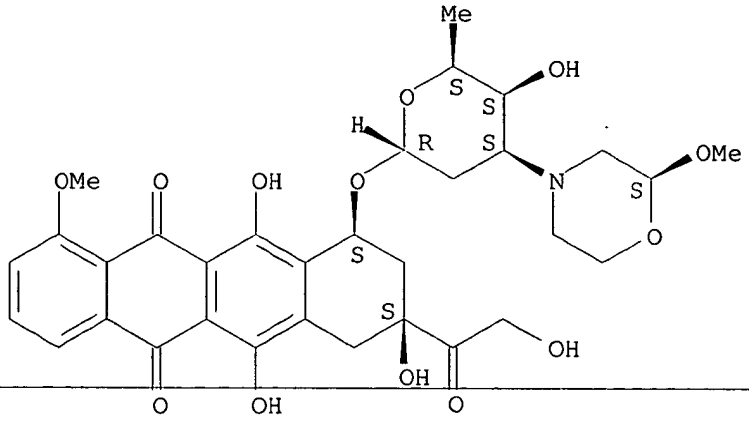
IT **108852-90-0**, PNU 152243
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**antitumor** activity and host toxicity of methoxymorpholinyl

doxorubicin: role of cytochrome P 450 3A)

RN 108852-90-0 HCAPLUS

CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-.alpha.-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

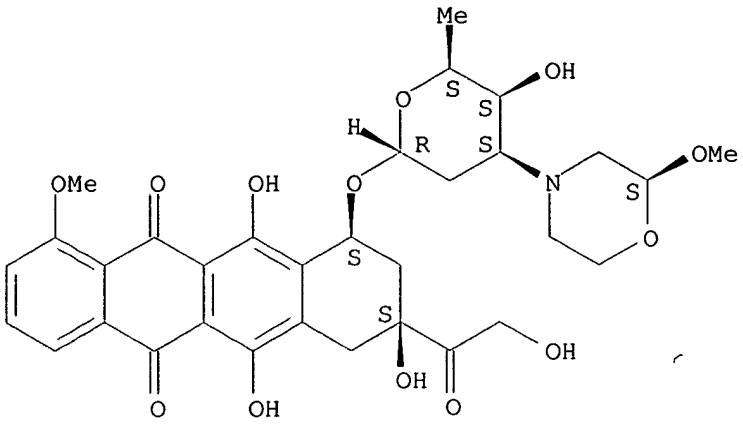


REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 7

L13 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:783213 HCAPLUS
DOCUMENT NUMBER: 132:245941
TITLE: Comparison of in vitro drug-sensitivity of human granulocyte-macrophage progenitors from two different origins: umbilical cord blood and bone marrow
AUTHOR(S): Gribaldo, Laura; Casati, Silvia; Castoldi, Anna F.; Pessina, Augusto
CORPORATE SOURCE: Institute for Health and Consumer Protection, ECVAM European Centre for the Validation of Alternative Methods, Ispra, 21020, Italy
SOURCE: Experimental Hematology (New York) (1999), 27(11), 1593-1598
CODEN: EXHMA6; ISSN: 0301-472X
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Predictive in vitro hematotoxicity assays using human cells will provide estn. of tolerable level and aid considerably the development of agents with greater therapeutic activity and less toxicity. Human hematopoietic cells can be derived from three sources: human bone marrow by sternal or femoral aspiration, mobilized peripheral blood, or umbilical cord blood samples collected from placentas after **deliveries**. Because of the difficulties to have a continuous supply of bone marrow cells from normal human donors and the related ethical problems, we performed a study to compare the sensitivity of human bone marrow cells (h-BMC) and human cord blood cells (h-CBC) to chems. to confirm if h-CBC can readily replace bone marrow cells in checking the sensitivity of GM-CFU progenitors to drugs as preliminarily reported in literature. Our results showed that the prediction of IC50 values in human model is quite similar by using h-BMC or h-CBC. On the contrary, the type of medium influenced in a significant way the ICs detn. of some drugs.
IT **108852-90-0**
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparison of in vitro drug-sensitivity of human granulocyte-macrophage progenitors from umbilical cord blood and bone marrow)
RN 108852-90-0 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-.alpha.-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

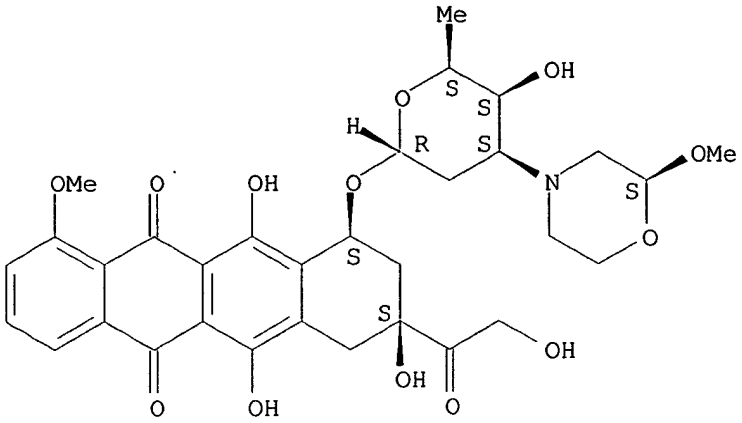
=> d ibib abs hitstr 8

L13 ANSWER 8 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:186967 HCAPLUS
DOCUMENT NUMBER: 131:39313
TITLE: **Delivery** of methoxymorpholinyl doxorubicin by interleukin 2-activated NK cells: effect in mice bearing hepatic **metastases**
AUTHOR(S): Quintieri, L.; Rosato, A.; Amboldi, N.; Vizler, C.; Ballinari, D.; Zanovello, P.; Collavo, D.
CORPORATE SOURCE: Department of Oncology and Surgical Sciences, University of Padova, Padua, 35128, Italy
SOURCE: British Journal of Cancer (1999), 79(7/8), 1067-1073
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The possibility of using interleukin 2 (IL-2)-activated natural killer cells (A-NK) to carry methoxymorpholinyl doxorubicin (MMDX; PNU 152243) to **liver**-infiltrating **tumors** was explored in mice bearing 2-day established M5076 reticulum cell sarcoma hepatic **metastases**. In vitro, MMDX was 5.5-fold more potent than doxorubicin against M5076 **tumor** cells. MMDX uptake by A-NK cells correlated linearly with drug concn. in the incubation medium [correlation coeff. (r) = 0.999]; furthermore, as MMDX incorporation was readily reproducible in different expts., the amt. of drug **delivered** by A-NK cells could be modulated. In vivo expts. showed that i.v. injection of MMDX-loaded A-NK cells exerted a greater therapeutic effect than equiv. or even higher doses of free drug. The increase in lifespan (ILS) following A-NK cell **delivery** of 53 .mu.g kg-1 MMDX, a dosage that is ineffective when administered in free form, was similar to that obsd. in response to 92 .mu.g kg-1 free drug, a dosage close to the 10% LD (ILS 42% vs. 38%, resp.). These results correlated with pharmacokinetic studies showing that MMDX encapsulation in A-NK cells strongly modifies its organ distribution and targets it to tissues in which IL-2-activated lymphocytes are preferentially entrapped after i.v. injection.

IT **108852-90-0**
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**delivery** of methoxymorpholinyl doxorubicin by interleukin 2-activated NK cells and its effect in mice bearing hepatic **metastases**)
RN 108852-90-0 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-.alpha.-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

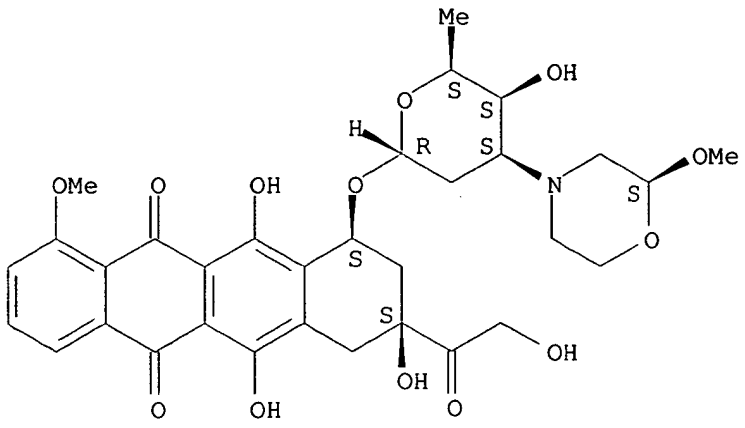


REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 9

L13 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:468189 HCAPLUS
DOCUMENT NUMBER: 129:211400
TITLE: Hematotoxicity on human bone marrow- and umbilical cord blood-derived progenitor cells and in vitro therapeutic index of methoxymorpholinyldoxorubicin and its metabolites
AUTHOR(S): Ghielmini, Michele; Colli, Emilia; Bosshard, Giovanna; Pennella, Giulia; Geroni, Cristina; Torri, Valter; D'Incalci, Maurizio; Cavalli, Franco; Sessa, Cristiana
CORPORATE SOURCE: Servizio Oncologico Cantonale, Ospedale S. Giovanni, Bellinzona, CH-6500, Switz.
SOURCE: Cancer Chemotherapy and Pharmacology (1998), 42(3), 235-240
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The toxic concn. of a 1-h period of exposure to doxorubicin (DX), {3'-deamino-3'-[2(S)-methoxy-4-morpholinyl]doxorubicin} (MMDX), and bioactivated MMDX on hematopoietic progenitors and **tumor** cell lines was detd. in vitro. Human bone marrow (BM) cells were twice as sensitive as human cord blood-derived (hCB) clonogenic cells to cytotoxics, and MMDX was twice as toxic as DX against hCB cells. MMDX activated with normal rat **liver** microsomes and with dexamethasone-induced rat microsomes, resp. were 70 and 230 times more toxic than MMDX. DX and MMDX had 5-fold stronger activities on **tumor** cell lines than on granulocyte/macrophage colony-forming cells, whereas bioactivated MMDX showed comparable cytotoxicity against **tumor** cells and hematopoietic progenitors. MMDX metabolites were very potent but displayed a lower degree of **tumor** selectivity than MMDX.
IT **108852-90-0**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(methoxymorpholinyldoxorubicin and its metabolites hemotoxicity on human bone marrow- and umbilical cord blood-derived progenitor cells)
RN 108852-90-0 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-.alpha.-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.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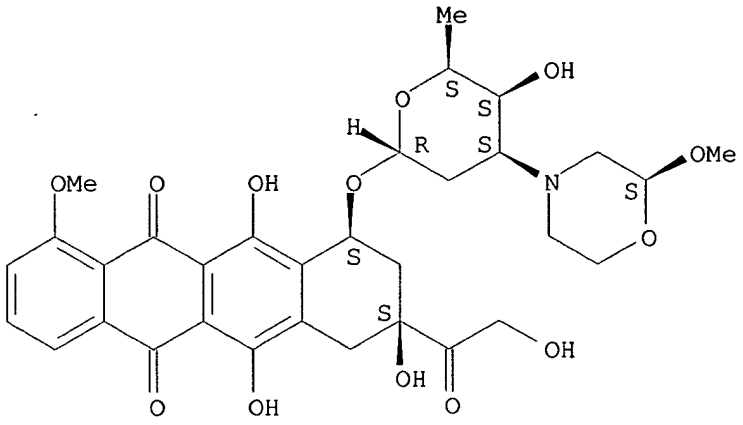
=> d ibib abs hitstr 10

L13 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:87389 HCAPLUS
DOCUMENT NUMBER: 128:200684
TITLE: Broad phase II and pharmacokinetic study of methoxymorpholino doxorubicin (FCE 23762-MMRDX) in non-small-cell lung cancer, renal cancer and other solid **tumor** patients
AUTHOR(S): Bakker, M.; Droz, J. P.; Hanauske, A. R.; Verweij, J.; Van Oosterom, A. T.; Groen, H. J. M.; Pacciarini, M. A.; Domenigoni, L.; Van Weissenbruch, F.; Pianezzola, E.; De Vries, E. G. E.
CORPORATE SOURCE: University Hospital Groningen, Groningen, 9700 RB, Neth.
SOURCE: British Journal of Cancer (1998), 77(1), 139-146
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The aim was to perform a broad phase II and pharmacokinetic study of methoxymorpholino-doxorubicin (MMRDX), a drug active against multidrug-resistant **tumor** cells in vitro when given by i.v. bolus at 1.5 mg m-2 every 4 wk, in metastatic or unresectable solid **tumor** patients with known intrinsic drug resistance. Patients received a max. of six cycles. Plasma, urine and leukocyte MMRDX and its 13-dihydro metabolite pharmacokinetic anal. was performed in patients without **liver metastases**. Patients (n = 48, 21 NSCLC, 19 renal cell, three head and neck **tumor**, three cervical cancer and two **adenocarcinoma** of unknown primary) received 132 cycles of MMRDX. Common toxicity criteria (CTC) grade III/**IV** thrombocytopenia (12% of cycles) and neutropenia (27% of cycles) occurred with median nadir on day 22. Transient transaminases elevation .gtoreq. grade III/**IV** was obsd. in 7% of cycles, late and prolonged nausea .gtoreq. grade II in 34% and vomiting .gtoreq. grade II in 39%. In two patients, the left ventricular ejection fraction was reduced .gtoreq. 15%. Of 37 evaluable patients, one out of 17 NSCLC had a partial response. Mean (.+-. s.d.) MMRDX AUC0.fwdarw..infin. calcd. up to 24 h after dosing was 20.4 .+-. 6.2 .mu.g h l-1 (n = 11) and t1/2' .gamma. was 44.2 h. Mean plasma clearance (.+-. s.d.) was 37.2 .+-. 7.3 l h-1 m-2 and vol. of distribution 1982 .+-. 64 l m-2. MMRDX leukocyte levels 2 and 24 h after **infusion** were 450 to 600-fold higher than corresponding MMRDX plasma levels. In urine, 2% of the MMRDX dose was excreted unchanged, and 2% as metabolite. The main side-effects of 1.5 mg m-2 every 4 wk of MMRDX are delayed nausea and vomiting and haematol. toxicity. MMRDX is characterized by extensive clearance and rapid and extensive distribution into tissues. A low response rate was obsd. in patients with **tumors** with intrinsic chemotherapy resistance.
IT **108852-90-0**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(methoxymorpholino doxorubicin (FCE 23762-MMRDX) in non-small-cell lung cancer, renal cancer and other solid **tumors** in humans)
RN 108852-90-0 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-.alpha.-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA

INDEX NAME)

Absolute stereochemistry.



=> d ibib abs hitstr 11

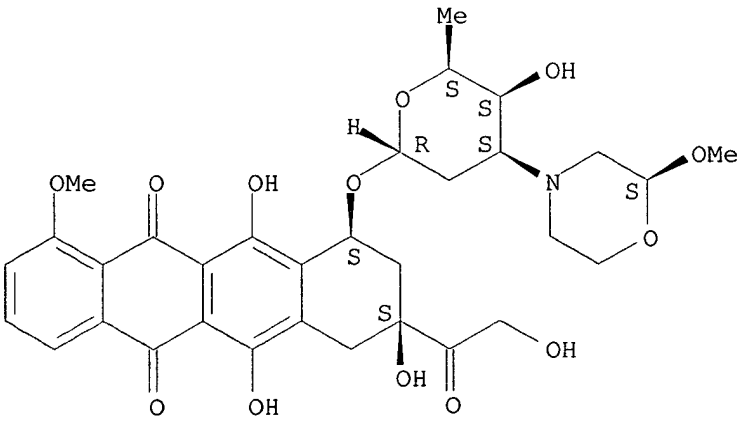
L13 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:644991 HCAPLUS
DOCUMENT NUMBER: 121:244991
TITLE: Metabolic conversion of methoxymorpholinyldoxorubicin: from a DNA strand breaker to a DNA cross-linker
AUTHOR(S): Lau, D.H.M.; Duran, G.E.; Lewis, A.D.; Sikic, B.I.
CORPORATE SOURCE: Division of Hematology/Oncology, University of California, CA, 95817, USA
SOURCE: Br. J. Cancer (1994), 70(1), 79-84
CODEN: BJCAAI; ISSN: 0007-0920
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Methoxymorpholinyldoxorubicin (MMDX) is a novel anti-cancer anthracycline that differs from doxorubicin in its mechanisms of action, pattern of resistance and metab. Whereas doxorubicin is primarily an inhibitor of topoisomerase II, MMDX inhibits both topoisomerases I and II, resulting in predominantly single-strand DNA cleavage and, to a lesser extent, double-strand DNA breakage. MMDX is equally cytotoxic in vitro against the doxorubicin-sensitive and -resistant uterine sarcoma cell lines, MES-SA and D .times. 5. Using fluorescent laser cytometry, MMDX was retained intracellularly to a similar extent in MES-SA and D .times. 5; the intracellular retention of MMDX was 7.5-fold higher than that of doxorubicin in D .times. 5. The cytotoxicity of MMDX on an ovarian **carcinoma** cell line, ES-2, was potentiated 50-fold by preincubating the drug with human **liver** microsomes and NADPH. This cytotoxic potentiation was assocd. with the appearance of DNA interstrand cross-links. The in vitro potentiation of MMDX was inhibited by cyclosporin A, which is a substrate for human cytochrome P 450 IIIA.

IT **108852-90-0**, FCE 23762
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(mechanism of cytotoxicity potentiation of methoxymorpholinyldoxorubicin)

RN 108852-90-0 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-.alpha.-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> d ibib abs hitstr 12

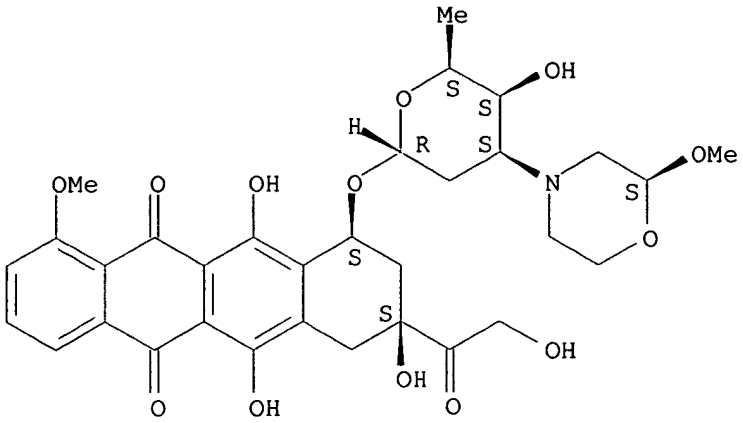
L13 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:621172 HCAPLUS
DOCUMENT NUMBER: 121:221172
TITLE: Effects of the methoxymorpholino derivative of doxorubicin and its bioactivated form versus doxorubicin on human leukemia and lymphoma cell lines and normal bone marrow
AUTHOR(S): Kuhl, Jorn-Sven; Duran, George E.; Chao, Nelson J.; Sikic, Branimir I.
CORPORATE SOURCE: Oncol. Div., Standford Univ. Sch. Med., Standford, CA, 94305, USA
SOURCE: Cancer Chemother. Pharmacol. (1993), 33(1), 10-16
CODEN: CCPHDZ; ISSN: 0344-5704
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The methoxymorpholino deriv. of doxorubicin (MMDX; FCE 23762) has recently entered clin. trials because of its broad spectrum of preclin. **antitumor** activity and non-cross-resistance in multidrug-resistant (MDR) **tumor** models. MMDX is activated in the **liver** to a >10 times more potent metabolite that cross-links DNA. To assess the potential of this drug in hematol. malignancies, we studied the myelotoxicity in vitro and **antitumor** effect of MMDX as well as its bioactivated form (MMDX+) in a panel of 14 different human leukemia and lymphoma cell lines. The **tumor** specificity of MMDX in CEM and K562 cells was similar to that of doxorubicin (DOX), and that of MMDX+ was slightly superior. All of the 14 cell lines were found to be more sensitive to MMDX and MMDX+ than were granulocyte-macrophage progenitors. On a molar basis, MMDX was approx. 3-100 times more active than DOX, and MMDX+ was 10-1,000 times more potent than DOX. The cytotoxic effect of MMDX and MMDX+ in two P-glycoprotein-pos. MDR sublines was greatly improved in comparison with that of DOX. Whereas the response to DOX in the different leukemia and lymphoma cell lines was highly heterogeneous, the response to MMDX and MMDX+ was rather homogeneous. The novel anthracycline MMDX and its bioactivated from MMDX+ are highly active against this panel of human leukemia and lymphoma cell lines and demonstrate potentially greater selectivity for **tumor** cells in vitro as compared with normal bone marrow precursors.

IT **108852-90-0**, FCE 23762 **108852-90-0D**, FCE 23762, active metabolite
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(leukemia and lymphoma inhibition by and myelotoxicity of doxorubicin and its methoxymorpholino deriv. in human cell lines)

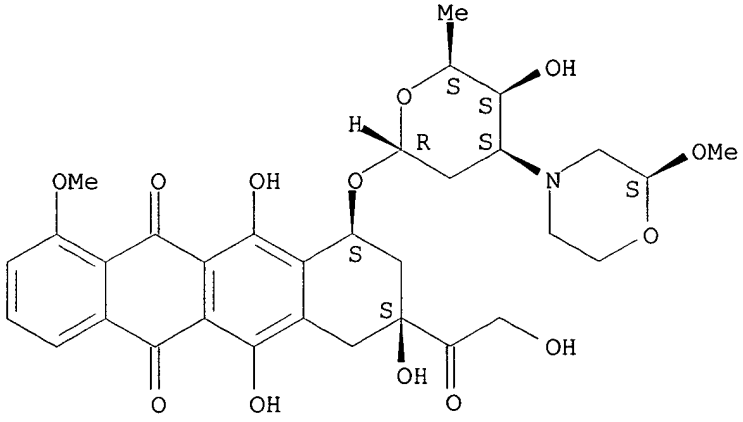
RN 108852-90-0 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-.alpha.-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 108852-90-0 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-.alpha.-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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L20 ANSWER 1 OF 21 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:142510 HCAPLUS
DOCUMENT NUMBER: 136:177968
TITLE: Remedies for cisplatin-tolerant cancer
INVENTOR(S): Kishimoto, Shuichi; Fukushima, Shoji; Takeuchi, Yoshikazu
PATENT ASSIGNEE(S): Sumitomo Pharmaceuticals Co., Ltd., Japan
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002013817	A1	20020221	WO 2001-JP6798	20010808
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001077711	A5	20020225	AU 2001-77711	20010808

PRIORITY APPLN. INFO.: JP 2000-244463 A 20000811
JP 2000-2000244463A 20000811
WO 2001-JP6798 W 20010808
OTHER SOURCE(S): MARPAT 136:177968
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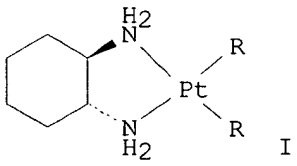

I

AB Prepns. wherein a fat-sol. platinum complex (I; R = (substituted) halogen) is dissolved or suspended in **iodized** opium **oil** fatty acid Et ester are efficacious as remedies for cisplatin-tolerant cancer.
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 2 OF 21 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:783033 HCAPLUS
DOCUMENT NUMBER: 136:123518
TITLE: Efficient and cancer-selective gene transfer to hepatocellular **carcinoma** in a rat using adenovirus vector with **iodized oil** esters
AUTHOR(S): Shiba, Hiroaki; Okamoto, Tomoyoshi; Futagawa, Yasuro; Ohashi, Toya; Eto, Yoshikatsu

CORPORATE SOURCE: Departments of Surgery and Gene Therapy, Institute of DNA Medicine, The Jikei University School of Medicine, Tokyo, 105-8461, Japan
SOURCE: Cancer Gene Therapy (2001), 8(10), 713-718
CODEN: CGTHEG; ISSN: 0929-1903
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Gene therapy for cancer requires efficient, selective gene transfer to cancer cells. In gene therapy for hepatocellular **carcinoma** (**HCC**), gene transfer is efficient for small **tumors**, but not for large **tumors**. The delivery of anticancer agents and of **iodized oil** esters as embolic agents through **tumor**-feeding arteries is known as transarterial embolization. We speculate that genes may be efficiently and selectively transferred for **HCC** using **iodized oil** esters because these esters may remain together with a genetic vector within **HCC** selectively. Hence, we have studied the effect of **iodized oil** esters on adenovirus vector-mediated gene transfer for **HCC** in vivo. A rat model of **HCC** induced with diethylnitrosamine and phenobarbital was injected with either AxCALacZ, which expresses the .beta.-galactosidase of Escherichia coli, or AxCALacZ and **iodized oil** esters into the **hepatic artery**. Histol. comparisons revealed that the .beta.-galactosidase expression in the rats with **HCC** injected with AxCALacZ and **iodized oil** esters was greater (P<.0001) in small **tumors** (P=.0046) and large **tumors** (P=.0023), and more selective (P=.0229) than in only AxCALacZ-injected rats. These results suggest that **iodized oil** esters are injected into **hepatic artery** together with adenovirus vector, and that genes may be efficiently and cancer-selectively transferred to **HCC**.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 3 OF 21 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:293923 HCAPLUS
DOCUMENT NUMBER: 135:200334
TITLE: Endovascular occlusion of branches of **hepatic artery** with poly(2-hydroxyethyl methacrylate) emboli as a single occlusive measure in hepatology
AUTHOR(S): Guseinov, Eldar; Horak, Daniel; Titova, Mariya; Adamyan, Arnold; Kokov, Leonid; Kubishkin, Valery; Vishnevskii, Vladimir; Skuba, Nikolai; Trostenyuk, Nadezhda
CORPORATE SOURCE: Inst. of Surgery, Russian Acad. of Med. Sciences, Russia
SOURCE: Polimery w Medycynie (2000), 30(3-4), 65-81
CODEN: PMYMAX; ISSN: 0370-0747
PUBLISHER: Zaklad Chirurgi Eksperymentalnej i Badania Biomaterialow Katedry Chirurgii Urazowej Akademii Medycznej
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A study was conducted to use embolization with poly(2-hydroxyethyl methacrylate) [poly(HEMA)] particles as a single occlusive measure in hepatol. in the treatment of hemangiomas and bleedings of complex genesis, and to take advantage of chemoembolization in the treatment of malignant **hepatic tumors**. Also, the embolization curing effect was evaluated by analyzing cells of the affected tissue isolated by the

liver puncture. Promising long-term results were obtained using chemoembolization as a single method of treatment of inoperable malignant **hepatic tumors** such as hepatocellular **carcinoma** assocd. with pronounced cirrhosis and **metastases** into the **liver**. Chemoembolization consisted of transcatheter **infusion** of 5-fluorouracil into the sick **liver** tissue within 3 days, combined with the injection of a mixt. of doxorubicin and **iodized oil**. While 5-fluorouracil leaked into the surrounding healthy tissues, Lipiodol acted as a regional embolic agent restricting the leakage of the toxic anticancer drug into the other organs. The therapy was followed by the complete occlusion of **tumor**-feeding arteries with poly(HEMA) hydrogel particles. Embolization arrested both benign and malignant **tumor** progression. **Tumor** regression developed due to the redn. of blood flow into the **tumor** on the one hand and as a consequence of a direct action of anticancer drug on the lesion on the other. Cytol. verification of focal **liver** lesions was an integral part of the therapeutical process, since it afforded indications for the surgical, endovascular and puncture interventions in the **liver** and monitored **tumor** regression. A distinctive feature of cytol. anal. of focal alterations in **liver** consisted of its simplicity and a high diagnostic accuracy. Moreover, the results were provided in a short time. In such a way, superselective catheterization and chemoembolization playing a potential therapeutic role in the management of **hepatic tumors** are available to the interventional radiologist. They combine diagnostic potentials with the independent therapeutic operation thus improving and extending life. Embolization with poly(HEMA) hydrogel particles in combination with an **infusion** of anticancer drugs may be the treatment of choice for a patient with large non-resectable **hepatic** lesions.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 4 OF 21 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:899011 HCAPLUS
DOCUMENT NUMBER: 135:55571
TITLE: The effect of different interventional treatment on P-glycoprotein in different histopathological types and grades of primary hepatocellular **carcinoma**
AUTHOR(S): Xiao, Enhua; Hu, Guodong; Liu, Pengcheng; Hu, Daoyu; Liu, Shaochun; Hao, Chunrong
CORPORATE SOURCE: Department of Radiology, Tongji Hospital, Tongji Medical University, Wuhan, 430030, Peop. Rep. China
SOURCE: Journal of Tongji Medical University (2000), 20(3), 231-234
CODEN: JTMUEI; ISSN: 0257-716X
PUBLISHER: Tongji Medical University
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To study the effect of the different interventional treatment on P-Glycoprotein (Pgp) in different histopathol. types of primary hepatocellular **carcinoma** (PHC), 98 surgically and histol. verified PHC specimens were obtained. The patients included 57 patients treated by surgical resection alone and 41 patients receiving 2nd-stage surgical resection after 4 kinds of interventional treatment. SABC immunohistochem. staining with a monoclonal antibody against human Pgp was used to observe the Pgp in all specimens. The pos. rate of Pgp was 100 % in group of chemotherapy alone, 62.5 % in group of chemotherapy combined with **iodized oil**, 46.6 % in group of chemotherapy combined with **iodized oil** and spongia gelatini

absorbens (Sga), 18.18 % in group of chemotherapy combined with EtOH-**iodized-oil** and Sga, and 52.63 % in group of surgical resection alone. The pos. rate of Pgp varied with different histopathol. types, with rate of clear cell PHC being the lowest, and that of poorly differentiated or undifferentiated PHC the highest. The pos. rate of Pgp was increased as pathol. grades increased. Overexpression of Pgp may be responsible for the intrinsic and acquired drug resistance of PHC. Multidrug resistance (MDR) varied with different histol. types. Therapy of PHC should be tailored according to individual. Local chemotherapy combined with EtOH-**iodized-oil** and Sga embolization may become a new way to overcome MDR of PHC.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 5 OF 21 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:263422 HCAPLUS
DOCUMENT NUMBER: 132:274031
TITLE: Transcatheter arterial chemoembolization therapy using **iodized oil** for patients with unresectable hepatocellular **carcinoma**: evaluation of three kinds of regimens and analysis of prognostic factors
AUTHOR(S): Ueno, Kazuto; Miyazono, Nobuaki; Inoue, Hiroki; Nishida, Hirotoshi; Kanetsuki, Ichiro; Nakajo, Masayuki
CORPORATE SOURCE: Department of Radiology, Faculty of Medicine, Kagoshima University, Kagoshima, 890-8520, Japan
SOURCE: Cancer (New York) (2000), 88(7), 1574-1581
CODEN: CANCAR; ISSN: 0008-543X
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The current study was conducted to evaluate retrospectively the effects of three kinds of regimens used in trans-catheter arterial chemoembolization (TACE) in patients with unresectable hepatocellular **carcinoma** (**HCC**) and patients' prognosis, and to analyze their prognostic factors. The study population was comprised of 152 patients who were treated by TACE alone. Three kinds of regimens were used successively: doxorubicin hydrochloride (ADM) and mitomycin C mixed with **iodized oil** in 26 patients (ADMOS group), a combination of cisplatin (CDDP) soln. and ADMOS in 70 patients (CDDP-ADMOS group), and CDDP powder and pirarubicin hydrochloride mixed with **iodized oil** in 56 patients (CTLS group). The CTLS group was comprised of patients with significantly worse background factors than the other two groups. The initial **tumor** response rate with a > 50% redn. was 12%, 23%, and 30%, resp., in the ADMOS, CDDP-ADMOS, and CTLS groups. CTLS was significantly more effective than ADMOS ($P < 0.05$), and slightly but not significantly better than CDDP-ADMOS ($P < 0.1$). The cumulative survival rates for the ADMOS, CDDP-ADMOS, and CTLS groups were 59.0%, 70.1%, and 72.0%, resp., at 1 yr; 0%, 16.3%, and 29.8%, resp., at 3 yr; and 0%, 4.1%, and 16.8%, resp., at 5 yr, with median survival times of 448 days, 574 days, and 758 days, resp. The CTLS group showed a slightly but not significantly better survival than the ADMOS and CDDP-ADMOS groups ($P < 0.1$). Multivariate anal. indicated that the significantly important prognostic factors (in order) were **extrahepatic metastasis** followed by the TACE regimen, serum .alpha.-fetoprotein levels, and portal vein involvement and that CTLS was the best of the three regimens. CONCLUSIONS. Although TACE, using an effective regimen, improves clin. results, **tumor** factors appear to be more important when detg. prognosis.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 6 OF 21 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:228866 HCAPLUS
DOCUMENT NUMBER: 132:231637
TITLE: **Hepatic** arterial chemoembolization with streptozotocin in patients with metastatic digestive endocrine **tumors**
AUTHOR(S): Dominguez, Sophie; Denys, Alban; Madeira, Idalina; Hammel, Pascal; Vilgrain, Valerie; Menu, Yves; Bernades, Pierre; Ruszniewski, Philippe
CORPORATE SOURCE: Federation of Hepato-Gastroenterology, Hopital Beaujon, Clichy, 92118, Fr.
SOURCE: European Journal of Gastroenterology & Hepatology (2000), 12(2), 151-157
CODEN: EJGHES; ISSN: 0954-691X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Hepatic** arterial chemoembolization (CE) with anthracyclines is an effective treatment for progressive **liver metastases** of digestive endocrine **tumors**. Streptozotocin (STZ) is widely used for systemic chemotherapy, but its efficacy by the **hepatic** arterial route has not been evaluated. Fifteen consecutive patients, mean age 57.8 yr, were prospectively included between July 1993 and Jan. 1997. All patients had progressive **liver metastases** from either a carcinoid **tumor** (eight patients) or an islet cell **carcinoma** (ICC) (seven patients) that had increased in size (.gtoreq. 25%) before CE. Five patients had the carcinoid syndrome. STZ was administered, as an emulsion with **iodized oil**, into the **hepatic artery** before embolization with gelatin sponge particles. Two to six procedures (median, 3) were performed in 12 patients (one in three patients). Changes in the size of the **liver metastases** were evaluated by CT scan or MRI according to WHO criteria. The median follow-up was 15 mo (1-50). An objective response was achieved in 8/15 patients (53%; median duration of 10.5 mo) whatever the primary **tumor** (carcinoid or ICC). The carcinoid syndrome disappeared in 3/5 patients for 10, 11 and 17 mo, resp. CE effectively controlled hypoglycemic attacks (decrease of > 50%) in the patient with insulinoma. The biol. response was complete in four patients for a median duration of 7 mo. CE induced minor side effects, namely nausea, fever and abdominal pain. Acute and reversible tubular necrosis due to CE was obsd. in one patient who had previously undergone a nephrectomy. **Hepatic** arterial chemoembolization with STZ is an effective treatment for patients with **liver metastases** caused by digestive endocrine **tumors**.

L20 ANSWER 7 OF 21 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:190906 HCAPLUS
DOCUMENT NUMBER: 132:231945
TITLE: **Intrahepatic** administration of methoxymorpholinodoxorubicin for the treatment of a **liver tumor**
INVENTOR(S): Pacciarini, Maria Adele; Valota, Olga; Kerr, David
PATENT ASSIGNEE(S): Pharmacia & Upjohn S.P.A., Italy
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000015203	A2	20000323	WO 1999-EP6298	19990827
WO 2000015203	A3	20000720		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9957421	A1	20000403	AU 1999-57421	19990827
BR 9913627	A	20010522	BR 1999-13627	19990827
EP 1112066	A2	20010704	EP 1999-944533	19990827
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002524496	T2	20020806	JP 2000-569787	19990827
NO 2001001116	A	20010514	NO 2001-1116	20010305
PRIORITY APPLN. INFO.:			GB 1998-20012 A	19980914
			WO 1999-EP6298 W	19990827

AB The invention discloses the use of methoxymorpholinodoxorubicin for the treatment of a **liver** cancer; in particular, it discloses the **intrahepatic** administration of methoxymorpholinodoxorubicin for use in the **liver tumor** therapy, optionally in assocn. with an agent, e.g. **iodized oil**, which remains selectively in the **liver tumor** after its injection through the **hepatic artery**.

L20 ANSWER 8 OF 21 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:609766 HCAPLUS
DOCUMENT NUMBER: 131:225549
TITLE: **Hepatic** intraarterial 131I **iodized oil** for treatment of hepatocellular **carcinoma** in patients with impeded portal venous flow
AUTHOR(S): De Baere, Thierry; Taourel, Patrice; Tubiana, Jean Michel; Kuoch, Viseth; Ducreux, Michel; Lumbroso, Jean; Roche, Alain J.
CORPORATE SOURCE: Departments of Interventional Radiology, Institut Gustave Roussy, Villejuif, 94805, Fr.
SOURCE: Radiology (Oak Brook, Illinois) (1999), 212(3), 665-668
CODEN: RADLAX; ISSN: 0033-8419
PUBLISHER: Radiological Society of North America
DOCUMENT TYPE: Journal
LANGUAGE: English
AB PURPOSE: To evaluate the efficacy and safety of intraarterial **hepatic** iodine 131 **iodized oil** for treatment of hepatocellular **carcinoma** in patients with impeded portal venous flow. MATERIALS AND METHODS: Twenty-four patients (mean age, 61 yr) with hepatocellular **carcinoma** underwent 38 courses of 131I **iodized oil** (one to three per patient), with a mean dose of 2,146 MBq injected into the proper **hepatic artery**. Hepatocellular **carcinoma** manifested as single nodules (n = 8; mean, 7.75 cm), multiple nodules (n = 13; mean, 5.46 cm), or a mass (n =

3) occupying more than two **hepatic** segments. Portal venous thrombosis was complete (n = 10), right (n = 9), left (n = 2), or multisegmental (n = 1). Two patients had hepatofugal portal flow. RESULTS: Among the 23 patients with evaluatable results, response to treatment was partial in three, and disease was stable in 12 and progressive in eight. Estd. actuarial survival rates were 70%, 33%, 12%, and 6% at 3, 6, 9, and 12 mo, resp., with two patients alive at 9 and 11 mo. The median survival time was 147 days. Adverse events were the early death of one patient owing to **hepatic** failure and transient symptomatic **hepatic** failure after 12 courses in nine patients. CONCLUSION: In this preliminary experience, intraarterial **hepatic** 131I **iodized oil** did not demonstrate high efficacy in the treatment of hepatocellular **carcinoma** in patients with portal venous thrombosis, as side effects were not rare.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 9 OF 21 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:734435 HCAPLUS
DOCUMENT NUMBER: 130:162799
TITLE: Analysis of the secondary resection effect of hepatocellular **carcinoma** after **hepatic** arterial chemoembolization
AUTHOR(S): Wang, Xiaolin; Gong, Gaoquan; Cheng, Jiemin; Yan, Zhiping; Li, Maoquan; Wang, Jianhua
CORPORATE SOURCE: Department of Raidiology, Zhongshan Hospital, Shanghai Medical University, Shanghai, 200032, Peop. Rep. China
SOURCE: Shanghai Yike Daxue Xuebao (1998), 25(5), 333-335, 339
CODEN: SYDXEE; ISSN: 0257-8131
PUBLISHER: Shanghai Kexue Jishu Chubanshe
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB Sixty-two patients treated by **hepatic** arterial chemoembolization (HAE) and sequential resection were divided into two groups, the no recurrence group (group A), and the recurrence group (group B) to evaluate the more suitable indication of secondary resection after **hepatic** arterial chemoembolization for patients with hepatocellular **carcinoma**. Statistical comparisons were made by Student's T test and Chi-square methods. The prognosis of the group A was better than that of the group B. The difference between the two groups was significant. The reaction to HAE, the **tumor** size and the no. of **intrahepatic** metastatic focus before operation were decreased ($P < 0.05$). There was no obvious correlation with HAE times, interval of HAE and also the level of AFP changes ($P > 0.05$). The results show that the complete accumulation of **iodized oil** in the **tumor** markedly decreasing in **tumor** size after HAE and no **intrahepatic** metastatic are the secondary reaction indication. HAE treatment should be performed no more than four times before resection and the interval between the final HAE and resection be no longer than four months.

L20 ANSWER 10 OF 21 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:812528 HCAPLUS
DOCUMENT NUMBER: 128:70502
TITLE: **Iodized oil** enhances the thermal effect of high-intensity focused ultrasound on ablating experimental **liver** cancer
AUTHOR(S): Cheng, Shu Qun; Zhou, Xin Da; Tang, Zhao You; Yu, Yao; Bao, Su Su; Qian, De Chu
CORPORATE SOURCE: Liver Cancer Institute, Zhong Shan Hospital, Shanghai

Medical University, Shanghai, 200032, Peop. Rep. China
SOURCE: Journal of Cancer Research and Clinical Oncology (1997), 123(11/12), 639-644
CODEN: JCROD7; ISSN: 0171-5216
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The influence of the biol. medium was studied on high-intensity focused ultrasound (HIFU) therapy for ablating exptl. **liver** cancer. The temp. rise in the focal zone in the presence of **iodized oil** or castor **oil** was obsd. in vitro. HIFU with **iodized oil** produced a higher and faster temp. rise than HIFU with castor oil. With excised **liver** samples, the temp. also rose higher and more rapidly and the target **liver** tissue revealed more radically and extensive destruction after injection of **iodized oil** into the **liver** than with castor oil. Nude mice bearing primary **liver** cancer LTNM4 implanted s.c., were left untreated (group I), injected with **iodized oil** alone (group II), received HIFU treatment (group III), or were exposed to HIFU after **iodized oil** injection (group **IV**). Inhibition of **tumor** growth was seen in groups III and **IV** as compared with groups I or II, the **tumor** growth inhibition rate on the 28th day after treatment being 87 and 93%, resp. Improved survival was noted in groups III and IV compared with groups I and II. Histol., group **IV** showed more complete **tumor** necrosis than did group III. These data suggest that HIFU combined with **iodized oil** may achieve synergism, location and targeting in the treatment of **liver** cancer.

L20 ANSWER 11 OF 21 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:739048 HCAPLUS
DOCUMENT NUMBER: 128:43537
TITLE: Prospective randomized trial of chemoembolization versus intra-arterial injection of 131I-labeled-**iodized oil** in the treatment of hepatocellular **carcinoma**
AUTHOR(S): Raoul, Jean-Luc; Guyader, Dominique; Bretagne, Jean-Francois; Heautot, Jean-Francois; Duvauferrier, Regis; Bourguet, Patrick; Bekhechi, Djemal; Deugnier, Yves M.; Gosselin, Michel
CORPORATE SOURCE: Service d'Hepatogastroenterologie, Hopital Pontchaillou, Centre Hospitalier Regional Universitaire, Rennes, 35033, Fr.
SOURCE: Hepatology (Philadelphia) (1997), 26(5), 1156-1161
CODEN: HPTLD9; ISSN: 0270-9139
PUBLISHER: Saunders
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Intra-arterial injection of radioactive Lipiodol has shown promising results in patients with hepatocellular **carcinoma** (**HCC**) and portal obstruction. The aim of this prospective, randomized trial was to compare the efficacy and tolerance of 131I-labeled Lipiodol and chemoembolization for the treatment of patients with **HCC**. From Sept. 1990 to Sept. 1993, 142 patients (135 men, 7 women; age: 65 .+-. 6.6 yr) were randomly assigned to treatment groups and given either intra-arterial injections of 131I-labeled Lipiodol (60 mCi; 2.2 GBq) (n = 73) or chemoembolization (70 mg cisplatin) (n = 69). Subsequent injections were given at 2, 5, 8, 12, and 18 mo. **Tumor** response was assessed on the basis of **tumor** size and serum .alpha.-fetoprotein levels. Patient tolerance was assessed clin. and

angiog. Survival rate was the main end-point. A total of 129 patients (65 in the 131I-labeled Lipiodol group and 64 in the chemoembolization group) were available for anal.; 13 were excluded, mainly because of portal vein thrombosis. The two groups were comparable. Actuarial survival curves were not significantly different between the two groups. Overall survival rates at 6 mo, 1, 2, 3, and 4 yr were 69%, 38%, 22%, 14%, and 10%, and 66%, 42%, 22%, 3%, and 0% in the 131I-labeled Lipiodol and chemoembolization groups, resp. Redn. in **tumor** size was similar for the two groups, with complete response in 1 and 0 patients and partial response in 15 and 16 patients in the 131I-labeled Lipiodol and chemoembolization groups, resp. Tolerance was significantly better in the 131I-labeled Lipiodol group both clin. (3 severe side effects vs. 29 in the chemoembolization group; $P < .001$) and angiog. (1 arterial thrombosis vs. 10 in the chemoembolization group; $P < .01$). In terms of patient survival and **tumor** response, radioactive 131I-labeled Lipiodol and chemoembolization were equally effective in the treatment of **HCC**, but tolerance to 131I-labeled Lipiodol was significantly better.

L20 ANSWER 12 OF 21 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:46461 HCAPLUS
DOCUMENT NUMBER: 126:86544
TITLE: Quantification of **tumor** uptake of ~~iodized oils and emulsions of~~ **iodized oils**: experimental study
AUTHOR(S): de Baere, Thierry; Zhang, Xiaowei; Aubert, Bernard; Harry, Gerald; Lagrange, Christine; Ropers, Jacques; Dufaux, Jacques; Lumbroso, Jean; Rougier, Philippe; Ducreux, Michel; Roche, Alain
CORPORATE SOURCE: Departments of Interventional Radiology, Institut Gustave Roussy, Fr.
SOURCE: Radiology (Oak Brook, Illinois) (1996), 201(3), 731-735
CODEN: RADLAX; ISSN: 0033-8419
PUBLISHER: Radiological Society of North America
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The purpose of this study was to optimize use of **iodized oil** for diagnostic computed tomog. (CT) enhanced with **iodized oil** and and for interstitial radiation therapy with iodine-131-labeled **iodized oil**, the authors quantified the distribution of **iodized oil** after injection of different formulations of **iodized oil** into the **hepatic artery**. I-125 labeled iodinated Et ester of poppyseed **oil** in two viscosities (**iodized oil** ultrafluid [viscosity, 0.04 Pa/s]) was injected (pure forms and three different emulsions of each) in to the **hepatic artery** of rabbits bearing VX2 **tumors** in the **liver**. All rabbits received a radiation dose of 4 Bq per kg of body wt. in 0.1 mL/kg **iodized oil**. Animals were killed 4 days later, and **iodized oil** uptake was evaluated in the **tumor, nontumorous liver** , and lung. There were no statistically significant differences in uptake between pure **iodized oil** ultrafluid or fluid or between the same type of emulsions made with each type of **iodized oil**. Lung uptake was significantly higher with pure **iodized oil** ultrafluid and fluid (19.75 kGq/g.+-.3.25[std. error of the mean] vs 19.48 kBq/g.+-. 6.15, resp.) than any emulsions (range, 3.72-8.14 kGq/g; mean, 5.68kGq/g) except the small-droplet oil-in-water emulsion (10.51 kBq/g.+-.1.18). The ratio of

tumor to **nontumorous liver** uptake of **iodized oil** was significantly higher with large-drop-.let water-in-**oil** emulsion made of **iodized oil** ultrafluid or fluid (10.26.+-.2.88 and 9.53.+-.0.64, resp.) than with any other product (range, 4.07-5.38;mean 4.49). Use of large-droplet water-in-oil emulsions limited lung uptake and increased **tumor** uptake of **iodized oil** after intraarterial **hepatic** injection in rabbits bearing VX2 **tumors** in the **liver**.

L20 ANSWER 13 OF 21 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:698704 HCAPLUS
DOCUMENT NUMBER: 126:70
TITLE: Treatment of unresectable hepatocellular **carcinoma**: Targeted therapies using **iodized oil**
AUTHOR(S): Bhattacharya, S.; Dusheiko, G. M.
CORPORATE SOURCE: Royal Free Hospital, University Departments Surgery, London, NW3 2QG, UK
SOURCE: Proceedings of the International Symposium of the Princess Takamatsu Cancer Research Fund (1995), Volume Date 1994, 25th(Hepatitis C Virus and Its Involvement in the Development of Hepatocellular Carcinoma), 253-264
CODEN: PPTCBY
PUBLISHER: Princeton Scientific
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with over 60 refs. Arterially administered **iodized oil** (Lipiodol) localizes selectively in **HCCs** for prolonged periods. Lipiodol-based intra-arterial chemotherapy and chemoembolization have yielded **tumor** response rates and survival benefits better than those offered by other therapies for unresectable Okuda Stage I and II **HCC**. Further trials are indicated to compare the different Lipiodol-cytotoxic embolic regimens available. Early results of Lipiodol-targeted radiotherapy are available. This is a promising therapeutic development, and warrants comparison with chemoembolization in a large prospective randomized trial.

L20 ANSWER 14 OF 21 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:276913 HCAPLUS
DOCUMENT NUMBER: 124:331526
TITLE: Human **liver** cancer cells and endothelial cells incorporate **iodized oil**
AUTHOR(S): Bhattacharya, S.; Dhillon, A. P.; Winslet, M. C.; Davidson, B. R.; Shukla, N.; Gupta, S. Datta; Al-Mufti, R.; Hobbs, K. E. F.
CORPORATE SOURCE: University Departments Surgery, Royal Free Hospital, London, NW3 2QG, UK
SOURCE: British Journal of Cancer (1996), 73(7), 877-81
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Iodized oil** (lipiodol) administered via the **hepatic artery** localizes selectively in primary **liver** cell cancers (hepatocellular **carcinomas** or **HCCs**) for prolonged periods and has been used as a vehicle for cytotoxic agents. Despite clin. use, the mechanism of lipiodol retention by **tumors** has remained unclear, embolization of oil droplets in

the **tumor** vasculature being the prevailing hypothesis. We have investigated the role of **tumor** and endothelial cells in lipiodol retention. Human **liver tumor** (Hep G2) cells and human umbilical vein endothelial cells in culture were exposed to lipiodol. Light microscopy using selective silver impregnation stains and TEM revealed lipiodol incorporation by both cell types, probably by pinocytosis. This was not assocd. with cellular injury in terms of cell lysis, cell replication or radio-labeled leucine uptake. Histol. anal. of 24 **HCCs** either surgically resected or discovered incidentally at **liver** transplantation (with prior arterial injection of lipiodol) revealed vesicles of lipiodol in the cytoplasm of **tumor** cells and endothelial cells lining **tumor** vessels. Thus, lipiodol is likely to deliver cytotoxic agents directly into **tumor** cells and endothelial cells, both in vitro and in vivo. This may also apply to other lipids and to other human **tumors**. These findings have significant therapeutic implications.

L20 ANSWER 15 OF 21 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:47219 HCAPLUS
DOCUMENT NUMBER: 124:169484
TITLE: Epirubicin-lipiodol chemotherapy versus 131iodine-lipiodol radiotherapy in the treatment of unresectable hepatocellular **carcinoma**
AUTHOR(S): Bhattacharya, Satyajit; Novell, J. Richard; Dusheiko, Geoffrey M.; Hilson, Andrew J.; Dick, Robert; Hobbs, Kenneth E.
CORPORATE SOURCE: University Departments Surgery, Royal Free Hospital, London, UK
SOURCE: Cancer (New York) (1995), 76(11), 2202-10
CODEN: CANCAR; ISSN: 0008-543X
PUBLISHER: Lippincott-Raven
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Arterially administered **iodized oil** (Lipiodol) is selectively retained by hepatocellular **carcinomas** (**HCCs**), and has been used as a vehicle for delivery of therapeutic agents to these **tumors**. This study compared the efficacy of Lipiodol-targeted epirubicin chemotherapy with Lipiodol-131I radiotherapy. Patients with unresectable **HCC** receiving Lipiodol-epirubicin or Lipiodol-131I show good **tumor** localization, acceptable toxicity, and comparable survival benefit at 6 and 12 mo with either modality.

L20 ANSWER 16 OF 21 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:670368 HCAPLUS
DOCUMENT NUMBER: 123:102197
TITLE: Portal vein embolization with lipiodol for treatment of **hepatic carcinoma** - an experimental study
AUTHOR(S): Liu, Peng-Cheng; Guo, Jun-Yuan; Hu, Guo-Dong; Wang, Cheng-Yuan; Huang, Zhi-Cheng; Liu, Shao-Chun
CORPORATE SOURCE: Tongji Hospital, Tongji Medical University, Wuhan, Peop. Rep. China
SOURCE: Journal of Tongji Medical University (1995), 15(1), 55-8
CODEN: JTMUEI; ISSN: 0257-716X
PUBLISHER: Tongji Medical University
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A suspension of **iodized oil** and anticancer agent was injected into the portal veins of 20 rats with **hepatic**

carcinoma. Oil drops were seen in **tumor** cell lines, small blood vessels inside the cancer nest, the sinusoid, and the central veins. After injection of oil suspension through the portal vein the distal small vessels were embolized and necrotic changes of **tumor** cells and their subordinate normal **liver** cells were obsd. The results obtained in this expt. provided a good anatomical and pathol. basis for treating **liver** cancers with the portal vein embolization with chemotherapeutic agents.

L20 ANSWER 17 OF 21 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:290394 HCAPLUS
DOCUMENT NUMBER: 122:71269
TITLE: Pharmacokinetics of zinostatin stimalamer (YM 881) in animals (I): Plasma concentration, distribution and excretion in rats, dogs and VX2-hepatoma bearing rabbits
AUTHOR(S): Kikuchi, Yasuhiro; Ikeda, Chieko; Tanaka, Syohei; Ohmi, Yukio; Esumi, Yoshio; Takaichi, Matsuo; Jin, Yoshitaka; Tsutsumi, Shuichiro; Gunji, Shinobu; et al.
CORPORATE SOURCE: Infectious Disease and Immunology Research Laboratories, Yamanouchi Pharmaceutical Co., Ltd., Tsukuba, 305, Japan
SOURCE: Yakuri to Chiryo (1973-2000) (1994), 22(4), 1845-58
CODEN: YACHDS; ISSN: 0386-3603
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB After i.v. administration of 3H-zinostatin stimalamer (YM 881) to rats and dogs, immunoreactive YM 881 and radioactivity in plasma were eliminated in a biphasic manner. The t1/2,.beta. of immunoreactive YM 881 and radioactivity in plasma was 4.9 h and 8.7 h in rats, and 25.6 h and 43.9 h in dogs, resp. The excretion (urine + feces) of radioactivity for 30 days after i.v. administration was 42.1% of the dose in rats and 42.4% in dogs. In VX 2-hepatoma bearing rabbits administered intra-**hepatic** arterially with 3H-YM 881 suspended in **iodized** poppyseed **oil** fatty acid Et ester, the excretion of radioactivity for 30 days was 43.2% of the dose. In rats administered i.v. with YM 881, the immunoreactive YM 881 levels at 5 min post-dosing were highest in plasma, followed by kidney >> **liver**, lung, spleen > heart >> muscle. At 24 h post-dosing, no immunoreactive YM 881 was detected in tissues tested, except plasma, kidney and spleen. The immunoreactive YM 881 in tissues was eliminated rapidly. In rats administered i.v. with 3H-YM 881, the radioactivity at 5 min post-dosing was highest plasma, followed by **liver**, bone marrow, kidney, spleen and other tissues. A small amt. of the radioactivity distributed in brain, eyeballs, muscle and adipose tissue. In **liver**, kidney, spleen, bone marrow and lymph, the radioactivity was reached max. level at 10-24 h post-dosing. At 30 day the radioactivity in kidney, spleen, bone marrow and lymph were as high as 51-91% of the peak level, indicating elimination of the radioactivity in tissues was slow.

L20 ANSWER 18 OF 21 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:208559 HCAPLUS
DOCUMENT NUMBER: 118:208559
TITLE: Distribution and effect of **iodized** poppyseed **oil** in the **liver** after **hepatic artery** embolization: experimental study in several animal species
AUTHOR(S): Kan, Zuxing; Sato, Morio; Ivancey, Krassi; Uchida, Barry; Hedgpeth, Penny; Lunderquist, Anders; Rosch, Josef; Yamada, Ryusaku

CORPORATE SOURCE: Dep. Diagn. Radiol., Univ. Lund, Malmoe, S-214 01, Swed.
SOURCE: Radiology (Easton, Pa.) (1993), 186(3), 861-6
CODEN: RADLAX; ISSN: 0033-8419
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To define the **intrahepatic** distribution of **iodized** poppyseed **oil** and its effect on the **liver**, **hepatic artery** embolization (HAE) was performed in 5 mice, 12 rats, 4 rabbits, and 21 pigs with the **iodized oil** alone or in combination with gelatin sponge powder (GSPow) in 3 rats or gelatin sponge particles (GSPs) in 9 pigs. All mice, rats, and rabbits underwent radiog. of the upper abdomen and in vivo microscopy of the **hepatic** periphery during and immediately after injection at 1, 4, and 24 h later. All pigs underwent angiog. before and after HAE, as well as measurement of portal venous pressure before HAE and 15, 30, 45, and 60 min and 4 wk after HAE. Follow-up radiographs were obtained in 18 pigs. HAE performed with the **iodized oil** only was well tolerated by the **liver**, even when high doses were used, likely because of continuous flushing of the sinusoids by high blood flow from peripheral arterioles. When HAE was performed with the **iodized oil** and GSPow, this blood flow ceased and necrosis developed. The degree of necrosis after HAE with the **iodized oil** in combination with GSPs was directly assocd. with the dose of **iodized oil**. HAE performed with GSPs only did not cause damage.

L20 ANSWER 19 OF 21 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:139184 HCAPLUS
DOCUMENT NUMBER: 118:139184
TITLE: Disposition of epirubicin in an oily contrast medium after **intravenous** and intrahepato-arterial administration in **liver** cancer: A preliminary report
AUTHOR(S): Lee, K.; Chan, Kelvin; Leung, W. T.; Leung, N. W. Y.; Ho, S.; Chan, M.; Lau, C. C.; Tao, M.; Lau, W. Y.; Shiu, W.
CORPORATE SOURCE: Fac. Med., Chinese Univ. Hong Kong, Shatin, Hong Kong
SOURCE: Eur. J. Drug Metab. Pharmacokinet. (1992), 17(3), 221-6
CODEN: EJDPD2; ISSN: 0398-7639
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The present study reports findings on the disposition of epirubicin after an intrahepato-arterial administration of the Lipiodol-drug complex, prepd. by mixing the drug-aq. phase with the **iodized oil** by ultra-sonification, in 14 patients with histol. proven hepatoma or hepatomegaly with serum .alpha.-fetoprotein level above 500 .mu.g.L-1. The vol. of Lipiodol used was 5 mL and the epirubicin dose was 50 mg.m.-2. Blood samples were obtained at various time intervals up to 72 h post-dose. Serum concns. of epirubicin were measured by liq. chromatog. with fluorometric detection. The area under serum concn.-time curve (AUC0.infin.) was higher in the Lipiodol-epirubicin group while the clearance was faster and elimination t1/2 and mean residence time shorter in the plain epirubicion group. However, interindividual variation in metab. of epirubicin would affect serum level of the drug. In three patients who were given i.v. and intrahepato-arterial injections (90 mg.m-2) of plain epirubicin and Lipiodol-drug complex, the relative bioavailability of Lipiodol-epirubicin complex (F = 0.76 and 0.45) was lower than that of plain epirubicin (F = 0.80 and 0.73) in two patients

while it was approx. 100% (F = 1.06 and 1.20) in one patient. It is likely that **liver** function of the patients might be modified by the disease state over a period of 3 mo in the cross-over study. Further studies with larger patient samples are required to confirm if there is a targeting effect of the Lipiodol-drug complex toward hepatoma using a better formulation of the drug in Lipiodol.

L20 ANSWER 20 OF 21 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1992:527409 HCAPLUS
DOCUMENT NUMBER: 117:127409
TITLE: **Intrahepatic** microvascular changes after **intrahepatic** arterial injection of Lipiodol in normal and cirrhotic rat
AUTHOR(S): Ohkusa, Akihiko
CORPORATE SOURCE: Sch. Med., Kinki Univ., Osakasayama, 589, Japan
SOURCE: Nippon Igaku Hoshasen Gakkai Zasshi (1992), 52(6), 774-85
CODEN: NHGZAR; ISSN: 0048-0428
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB The effects of Lipiodol, **iodized oil**, used as an agent for diagnosis or treatment of **hepatic** malignancies, were examd. in rats by SEM. Injection of Lipiodol via the **intrahepatic** artery caused an impairment of capillary vessels in the peribiliary plexus to a greater degree in normal rats than in cirrhotic ones and proliferation of the perinodular arterial plexus and dilatation of the peribiliary plexus in cirrhotic rats.

L20 ANSWER 21 OF 21 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:88667 HCAPLUS
DOCUMENT NUMBER: 114:88667
TITLE: Slow-release drug delivery granules containing porous calcium phosphate
INVENTOR(S): Tsuru, Sumiaki; Tsugita, Masashi; Takasaki, Ken; Yokoo, Akihiko; Ichitsuka, Takeshi
PATENT ASSIGNEE(S): Asahi Optical Co., Ltd., Japan
SOURCE: Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 376331	A2	19900704	EP 1989-124107	19891228
EP 376331	A3	19910313		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 03218310	A2	19910925	JP 1989-343421	19891228
JP 2842647	B2	19990106		
US 5055307	A	19911008	US 1989-458310	19891228

PRIORITY APPLN. INFO.: JP 1988-335355 19881229
AB Slow-release granules comprises porous granules of a Ca phosphate (having a ratio of Ca to P of 1.3-1.8, a porosity of 0.1-70%, a sp. surface area of 0.1-50 m2/g, and a pore size of 1 nm-10.mu.m), calcined at 200-1400.degree., and impregnated with a drug component. The granules are further coated with a polymeric compd. selected from albumin, dextran, Et ester of **iodized** poppy seed **oil** fatty acid, gelatin, carboxymethyl chitin, and glycol chitin. The invention granules have a controllable and prolonged drug release effect and a good imaging property

to an x-ray or ultrasonic wave, therefore can be advantageously utilized in the field of a chemotherapy. Porous hydroxyapatite granules (Ca/P = 1.67; av. granular size 30 .mu.m; porosity 50%; av. pore size 90 nm; sp. surface area 23.0 m2/g), fired at 700.degree. were prepd. The granules (100 mg) were mixed with an aq. soln. of 10 mg Adriacin in 2 mL water to obtain the Adriacin-impregnated granules, which were freeze-dried at -70.degree. under 10-4-10-7 torr and suspended in a mixed soln. of 1 mL Conray (sodium iothalamate contrast medium) and 1 mL Lipiodol. The suspension 0.1 mL was injected to rats through a common **hepatic artery** and Adriacin residual amts. in the **liver** at 6, 24, and 48 h after injection were 49.8, 13.6, and 8.2%, resp., compared to 16.0, 14.8, and 1.1%, resp. with control compn. contg. Adriacin-Conray-Lipiodol mixt.

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L25 ANSWER 1 OF 17 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:641699 HCAPLUS
DOCUMENT NUMBER: 131:266539
TITLE: Phase I clinical and pharmacological study of oral methoxymorpholinyl doxorubicin (PNU 152243)
AUTHOR(S): Sessa, Cristiana; Zucchetti, Massimo; Ghielmini, Michele; Bauer, Jean; D'Incalci, Maurizio; De Jong, Jolanda; Naegele, Huguette; Rossi, Simona; Pacciarini, Maria Adele; Domenigoni, Letizia; Cavalli, Franco
CORPORATE SOURCE: Istituto Oncologico Svizzera Italiana, Division Oncology, Ospedale San Giovanni, Bellinzona, CH-6500, Switz.
SOURCE: Cancer Chemotherapy and Pharmacology (**1999**), 44(5), 403-410
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The methoxymorpholinyl doxorubicin analog PNU 152243 was brought into clin. studies because of preclin. observations of its non-cross-resistance in mdr tumor cells, dose-limiting neutropenia, lack of cardiotoxicity, and antitumor activity after oral administration. PNU 152243 was given orally every 4 wk to 21 adults with a variety of solid tumors at doses ranging from 59 to 940 .mu.g/m2. Antiemetic prophylaxis with 5-HT3 antagonists and steroids, given i.v. on day 1 and orally on days 2-8, was required beginning with the dose of 118 .mu.g/m2. The blood plasma pharmacokinetics of PNU 152243 were detd. by an HPLC method with fluorescence detection. The in vitro myelotoxic effects on granulocyte macrophage-colony forming cells (GM-CFC) of the plasma from 11 patients, obtained 4 and 6 h after treatment at all dose levels, were also assessed. Neutropenia was the main hematol. toxic effect and the max. tolerated dose (MTD) for myelotoxicity was 940 .mu.g/m2, with neutropenia grade 3-4 in 2 of 3 patients. Dose-dependent nausea and vomiting were dose-limiting and the MTD for gastrointestinal toxicity was fixed at 820 .mu.g/m2, with grade 4 vomiting in 1 of 2 patients. Other frequent toxic effects were diarrhea and fatigue. Peak levels of PNU 152243 were achieved 4 h after dosing. Dose-dependent Cmax and AUCExp, and interpatient variability of the main pharmacokinetic parameters were found. Very low levels of the 13-dihydrometabolite PNU 155051 were detected only at the highest doses. The hematotoxicity tests showed a <70% colony growth inhibition with no correlation between the growth inhibition effect and the degree of myelotoxicity in the same patient. Plasma concns. of PNU 152243 were 1000 times lower than the concn. inhibiting the growth of 70% of colonies. No objective tumor responses were seen. Owing to the occurrence of severe and prolonged nausea and vomiting, the clin. development of oral PNU 152243 was discontinued. The higher-than-expected neutropenia and its lack of relationship with plasma levels of PNU 152243 and its 13-dihydroderivative PNU 155051 might be related to the formation of potent cytotoxic metabolites present in human plasma at undetectable concns. and with prolonged half-life, as suggested by hematotoxicity tests performed with plasma from patients in GM-CFC assays.

IT **108852-90-0**, 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(2S)-2-methoxy-4-morpholinyl]-.alpha.-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)-
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)

(clin. and pharmacol. study of oral methoxymorpholinyl doxorubicin (PNU 152243))
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 2 OF 17 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:191827 HCAPLUS
DOCUMENT NUMBER: 130:320537
TITLE: The antitumor efficacy of cytotoxic drugs is potentiated by treatment with PNU 145156E, a growth-factor-complexing molecule
AUTHOR(S): Sola, Francesco; Capolongo, L.; Moneta, Donatella; Ubezio, Paolo; Grandi, Maria
CORPORATE SOURCE: Pharmacia Upjohn, Milan, I-20014, Italy
SOURCE: Cancer Chemotherapy and Pharmacology (**1999**), 43(3), 241-246
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB PNU 145156E (formerly FCE 26644) is a non-cytotoxic mol. whose antitumor activity is exerted through the formation of a reversible complex with growth/angiogenic factors, thus inhibiting their induction of angiogenesis. The in vitro and in vivo the activity of PNU 145156E was studied in combination with the 4 cytotoxic drugs doxorubicin, cyclophosphamide, methoxy-morpholinyl-doxorubicin (MMDX, FCE 23762, PNU 152243), and 9-aminocamptothecin against M5076 murine reticulosarcoma. In vitro, PNU 145156E did not modify the cytotoxicity of the 4 drugs or the cell-cycle block induced by doxorubicin. In vivo, at the optimal dose of each compd., the antitumor activity was increased in all combinations, with no assocd. increase in general toxicity being obsd. In healthy mice treated with cyclophosphamide or doxorubicin the assocn. with PNU 145156E did not enhance the myelotoxic effect induced by the 2 cytotoxics. These results indicate that 2 drugs affecting solid tumor growth through 2 different mechanisms - growth factor blockage and cell proliferation - can be combined, resulting in increased antitumor efficacy with no additive toxicity.
IT **108852-90-0**, FCE 23762
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antitumor efficacy of cytotoxic drugs is potentiated by treatment with PNU 145156E)
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 3 OF 17 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:128791 HCAPLUS
DOCUMENT NUMBER: 128:239074
TITLE: Nemorubicin: antineoplastic anthracycline
AUTHOR(S): Graul, A.; Leeson, P. A.; Castaner, J.
CORPORATE SOURCE: Prous Science Publishers, Barcelona, 08080, Spain
SOURCE: Drugs of the Future (**1997**), 22(12), 1319-1324
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: J. R. Prous, S.A.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Nemorubicin, a methoxymorpholino deriv. of doxorubicin, is a potent antitumor agent against leukemias and solid tumors. While the activity of

nemorubicin in vitro was only 3-5 times more potent than that of doxorubicin, its in vivo activity was 50-80-fold greater than that of the parent drug. Nemorubicin also possesses reduced cardiotoxicity compared to doxorubicin.

IT **108852-90-0P**, Nemorubicin
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(antitumor activity and cardiotoxicity of anthracycline nemorubicin)

L25 ANSWER 4 OF 17 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:777149 HCAPLUS
DOCUMENT NUMBER: 128:57192
TITLE: Mechanisms for high methoxymorpholino doxorubicin cytotoxicity in doxorubicin-resistant tumor cell lines
AUTHOR(S): Bakker, Marleen; Renes, Johan; Groenhuijzen, Anneke; Visser, Petra; Timmer-Bosscha, Hetty; Muller, Michael; Groen, Harry J. M.; Smit, Egbert F.; De Vries, Elisabeth G. E.
CORPORATE SOURCE: Department of Pulmonary Diseases, University Hospital Groningen, Groningen, Neth.
SOURCE: International Journal of Cancer (1997), 73(3), 362-366
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Methoxymorpholino doxorubicin (MMRDX) is an anthracycline analog that is able to overcome tumor cell resistance to classical anthracyclines. Mechanisms for increased MMRDX cytotoxicity were analyzed in a small cell lung carcinoma cell line (GLC4), its 300-fold doxorubicin-resistant and multidrug resistance-assocd. protein (MRP)-over-expressing subline (GLC4/ADR), an ovarian carcinoma cell line (A2780) and its 100-fold doxorubicin resistant and P-glycoprotein (P-gp)-over-expressing subline A2780AD. Cross-resistance, measured with the MTT assay at MMRDX concn. resulting in 50% growth inhibition, was 1.8-fold in GLC4/ADR and 4.5-fold in A2780AD compared to their resp. parental cell lines. Cellular MMRDX accumulation was equal in GLC4 and GLC4/ADR and 2-fold lower in A2780AD compared to A2780. Doxorubicin fluorescence was analyzed with confocal laser scan microscopy. Fluorescence was nuclear in sensitive, and cytoplasmic in resistant, cell lines, while MMRDX fluorescence was found in the nucleus in all cell lines. Pre-incubation with the MRP blocker MK571 restored in GLC4/ADR cells the nuclear doxorubicin fluorescence pattern, as obsd. in GLC4 cells. MMRDX, thus, can largely overcome cross-resistance in these P-gp- and MRP-overexpressing doxorubicin-resistant cell lines. Our results suggest that MMRDX is not a substrate for MRP-mediated resistance.

IT **108852-90-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(mechanisms for high methoxymorpholino doxorubicin cytotoxicity in doxorubicin-resistant tumor cell lines)

L25 ANSWER 5 OF 17 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:356264 HCAPLUS
DOCUMENT NUMBER: 127:104051
TITLE: In vitro antitumor activity of 3'-desamino-3'(2-

methoxy-4-morpholinyl) doxorubicin on human melanoma cells sensitive or resistant to triazene compounds

AUTHOR(S): Alvino, Ester; Gilberti, Sara; Cantagallo, Daniela; Massoud, Renato; Gatteschi, Antonietta; Tentori, Lucio; Bonmassar, Enzo; D'Atri, Stefania

CORPORATE SOURCE: Institute Experimental Medicine, National Council Research, Rome, I-00137, Italy

SOURCE: Cancer Chemotherapy and Pharmacology (**1997**), 40(2), 180-184
CODEN: CCPHDZ; ISSN: 0344-5704

PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new methoxymorpholinyl derivate of Adriamycin (ADR), FCE 23762 (MDR), has recently been selected for phase I clin. trials for its reduced cardiotoxicity and for its cytotoxic activity against a broad spectrum of solid tumors and leukemias that are sensitive or resistant to ADR. The purpose of the study was to compare the in vitro antitumor activity of MDR and ADR on human melanoma lines with different chemosensitivity to triazene compds., among which dacarbazine remains a ref. drug in the treatment of melanoma. MRD and ADR were tested in vitro on 3 melanoma lines previously screened for their chemosensitivity to the triazene compd. .rho.-(3-methyl-1-triazeno) benzoic acid, potassium salt (MTBA). The 3 lines were analyzed for P-170 expression, total glutathione (GSH) content, and GSH-related enzyme activity. All melanomas, whether sensitive or resistant to MTBA, were susceptible to antracycline treatment. The cytotoxic activity of MRD was comparable with that of ADR, and no substantial difference was found in cell growth inhibition between the 2 drugs.

IT **108852-90-0**, FCE 23762
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(in vitro antitumor activity of adriamycin deriv. FCE 23762 on human melanoma cells sensitive or resistant to triazene compds.)

L25 ANSWER 6 OF 17 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1996:714629 HCAPLUS
DOCUMENT NUMBER: 126:404

TITLE: Morpholinylanthracyclines: Cytotoxicity and antitumor activity of differently modified derivatives

AUTHOR(S): Ripamonti, Marina; Capolongo, Laura; Melegaro, Giulia; Gornati, Carlo; Bargiotti, Alberto; Caruso, Michele; Grandi, Maria; Suarato, Antonino

CORPORATE SOURCE: Oncology Department, Pharmacia Research Center, Milan, Italy

SOURCE: Investigational New Drugs (**1996**), 14(2), 139-144
CODEN: INNDDK; ISSN: 0167-6997

PUBLISHER: Kluwer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The relation between different chem. modifications on morpholinylanthracyclines and their ability to overcome multidrug resistance (MDR) has been evaluated testing all compds. in vitro on LoVo and LoVo/DX human colon adenocarcinoma cells and in vivo on disseminated P388 and P388/DX murine leukemias. Results obtained led us to the following conclusions: (1) the insertion of the morpholinyl or the methoxymorpholinyl group on position 3' of the sugar moiety confers the ability to overcome MDR in vitro and in vivo; conversely, 4' morpholinyl

compds. are effective on MDR cells only in vitro and result inactive in vivo on DX-resistant leukemia; (2) all chem. modifications performed on 3' morpholinyl or methoxymorpholinyl derivs., that is substitutions on the aglycon or on position 2 of the morpholino ring, do not interfere with the activity of the compds.: all derivs. present have the same efficacy on sensitive and resistant models. It is concluded that position 3' in the sugar moiety plays a crucial role in the ability of morpholinylanthracyclines to overcome MDR.

IT **108852-90-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(cytotoxicity and antitumor activity of differently modified morpholinylanthracycline derivs.)

L25 ANSWER 7 OF 17 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:691646 HCAPLUS
DOCUMENT NUMBER: 125:316524
TITLE: Overcoming PGP-related multidrug resistance. The cyclosporine derivative SDZ PSC 833 can abolish the resistance to methoxy-morpholynil-doxorubicin
AUTHOR(S): Michieli, Mariagrazia; Damiani, Daniela; Michelutti, Angela; Melli, Cristina; Ermacora, Anna; Geromin, Antonella; Fanin, Renato; Russo, Domenico; Baccarani, Michele
CORPORATE SOURCE: Department Clinical and Morphological Research, University Hospital, Udine, 33100, Italy
SOURCE: Haematologica (**1996**), 81(4), 295-301
CODEN: HAEMAX; ISSN: 0390-6078
PUBLISHER: Il Pensiero Scientifico
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The results obtained so far in studies designed to neutralize P glycoprotein (PGP)-related multidrug resistance (MDR) by using MDR reversal agents, have not yet fulfilled the promise of the expts. which were performed in vitro. To improve PGP-related MDR neutralization, we tested in vitro the activity of the cyclosporine deriv. SDZ PSC 833 (PSC) together with doxorubicin (DOX) and with two new DOX derivs. named 4' iodo 4' deoxy-doxorubicin (IODODOX) and methoxy-morpholynil-doxorubicin (MMDOX, FCE 23762) using four different human cell lines and their multi-drug resistant variants. Anthracycline toxicity was evaluated by using the MTT method after a 7-day culture with continuous exposure to the antitumor drugs with or without the addn. of PSC. PSC significantly down-modulated the toxicity of all three anthracyclines in all the four cell systems. However, despite the great increase caused by PSC in the toxicity of DOX and a more modest effect on the toxicity of the two DOX derivs., this MDR reversal agent could only completely block the PGP mediated MMDOX resistance whereas DOX refractoriness was only decreased. The combination of MMDOX or IODODOX with PSC 1.6 .mu.M is more efficient than the combination of DOX plus PSC for the full reversion of PGP-mediated drug resistance. Careful clin. studies are required to evaluate if these assocns. can also effectively and safely neutralize MDR in vivo.

IT **108852-90-0**, FCE 23762
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(combination of cyclosporine deriv. and doxorubicin derivs. in overcoming P-glycoprotein-related multidrug resistance in human cancer)

L25 ANSWER 8 OF 17 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1996:423567 HCAPLUS
DOCUMENT NUMBER: 125:131643
TITLE: Differential single- versus double-strand DNA breakage produced by doxorubicin and its morpholinyl analogs
AUTHOR(S): Duran, George E.; Lau, Derick H. M.; Lewis, Alexander D.; Kuhl, Jorn-S.; Bammler, Theodor K.; Sikic, Branimir I.
CORPORATE SOURCE: School Medicine, Stanford University, Stanford, CA, 94305-5306, USA
SOURCE: Cancer Chemotherapy and Pharmacology (**1996**), 38(3), 210-216
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The morpholinyl analogs of doxorubicin (DOX) have previously been reported to be non-cross-resistant in multidrug resistant (MDR) cells due to a lower affinity for P-glycoprotein relative to the parent compd. In order to further investigate the mechanisms of action of these morpholinyl anthracyclines, we examd. their ability to cause DNA single- and double-strand breaks (SSB, DSB) and their interactions with topoisomerases. Alk. elution curves were detd. after 2-h drug treatment at 0.5, 2 and 5 .mu.M, while neutral elution was conducted at 5, 10 and 25 .mu.M in a human ovarian cell line, ES-2. A pulse-field gel electrophoresis assay was used to confirm the neutral elution data under the same conditions. Further, K-SDS pptn. and topoisomerase drug inhibition assays were used to det. the effects of DOX and the morpholinyl analogs on topoisomerase (Topo) I and II. Under deproteinated elution conditions (pH 12.1), DOX, morpholinyl DOX (MRA), methoxymorpholinyl DOX (MMDX) and morpholinyl oxaunomycin (MX2) were equipotent at causing SSB in the human ovarian carcinoma cell line, ES-2. However, neutral elution (pH 9.6) under deproteinated conditions revealed marked differences in the degree of DNA DSB. After 2-h drug exposures at 10 .mu.M, DSBs were 3300 rad equiv. for MX2, 1500 for DOX and 400 for both MRA and MMDX in the ES-2 cell line. Pulsefield data substantiated these differences in DSBs, with breaks easily detected after MX2 and DOX treatment, but not with MRA and MMDX. DOX and MX2 thus cause DNA strand breaks selectively through interaction with Topo II, but not Topo I. In contrast, MRA and MMDX cause DNA breaks through interactions with both topoisomerases with a predominant inhibition of Topo I.

IT **108852-90-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(differential single- vs. double-strand DNA breakage produced by doxorubicin and its morpholinyl analogs)

L25 ANSWER 9 OF 17 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:274368 HCAPLUS
DOCUMENT NUMBER: 125:449
TITLE: Cellular uptake, cytotoxicity, and transport kinetics of anthracyclines in human sensitive and multidrug-resistant K562 cells
AUTHOR(S): Praet, Michel; Stryckmans, Pierre; Ruysschaert, Jean-Marie
CORPORATE SOURCE: Lab. Chimie-Physique Macromolecules Interfaces, Univ. Libre Bruxelles, Brussels, B1050, Belg.
SOURCE: Biochemical Pharmacology (**1996**), 51(10), 1341-1348
CODEN: BCPCA6; ISSN: 0006-2952

PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Multidrug resistance in tumor cells is often assocd. with the presence of an .apprx.170 kDa plasma membrane glycoprotein (Pgp) that acts as drug-efflux pump and decreases intracellular antitumor drug concn. We measured the uptake of seven anthracyclines (daunorubicin, doxorubicin, 4'-epi-doxorubicin, 4'-deoxy-doxorubicin, iododoxorubicin, 3'(3-methoxymorpholino)-doxorubicin (FCE23762) and 4-demethoxydaunorubicin) into K562 cells sensitive and resistant (K562/DNR) to daunorubicin. The K562/DNR subline expresses Pgp at the membrane surface, whereas its sensitive counterpart does not. Laser flow cytometry was used to quantitate intracellular anthracycline content. Uptake of daunorubicin, doxorubicin, 4'-epi-doxorubicin, and 4'-deoxy-doxorubicin was minimal in the K562/DNR subline as compared to their uptake in sensitive cells. On the contrary, iododoxorubicin, FCE23762, and 4-demethoxy-daunorubicin accumulate to nearly the same extent into sensitive and resistant K562 cells. Growth inhibition data indicated that the resistance factor for iododoxorubicin, FCE23762. and 4-demethoxy-daunorubicin is markedly decreased as compared to the other drugs. Fluorescence measurements were carried out to det. the kinetic parameters assocd. with the influx and efflux of the drugs into and out of K562 cells. Kinetic data indicated that iododoxorubicin, FCE23762, and 4-demethoxy-daunorubicin are not actively rejected from resistant cells, suggesting that they are poor substrates for Pgp-mediated transport. This observation is related to their ability to overcome the multidrug-resistant phenotype of K562/DNR cells in vitro.

IT **108852-90-0**, FCE23762
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(cellular uptake, cytotoxicity, and transport kinetics of anthracyclines in human sensitive and multidrug-resistant K562 cells)

L25 ANSWER 10 OF 17 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:865994 HCAPLUS
DOCUMENT NUMBER: 123:329262
TITLE: Structurally modified anthracyclines retain activity in a cell line with simultaneous typical and atypical multidrug resistance
AUTHOR(S): Bielack, Stefan S.; Kallenbach, Klaus; Looft, Guido; Erttmann, Rudolf; Winkler, Kurt
CORPORATE SOURCE: Department Pediatric Hematology and Oncology, Pediatric University Hospital, Hamburg, 20246, Germany
SOURCE: Anticancer Research (**1995**), 15(4), 1279-84
CODEN: ANTRD4; ISSN: 0250-7005
PUBLISHER: Anticancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Resistance to the classical anthracyclines may be due to one or several mechanisms, most notably p-glycoprotein (pGP) assocd. multidrug resistance (mdr1, "typical mdr") and altered activity of topoisomerase II (topo II) ("atypical mdr"). Modulators of mdr1 will be of limited value in case of combined forms of resistance. A Friend murine erythroleukemia cell line (F4-6R) carrying both mdr1 and topo II mediated anthracycline resistance was used to det. the efficacy of structurally altered anthracyclines against such extended multidrug resistance. Proliferation assays showed that 3'N-morpholinyl substituted anthracyclines were able to retain much of their activity even this setting. MX2 (KRN8602; 3'-deamino-3'-[4-morpholinyl]-13-deoxo-10-hydroxycarminomycin), which is 9-alkylated in

addn. to carrying a 3'N-morpholinyl group, was the most promising agent tested.

IT **108852-90-0**, FCE 23762
RL: PRP (Properties); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antitumor activity of modified anthracyclines in cell line with simultaneous typical and atypical multidrug resistance)

L25 ANSWER 11 OF 17 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:804875 HCAPLUS
DOCUMENT NUMBER: 123:275195
TITLE: Crystal structures of four morpholino-doxorubicin anticancer drugs complexed with d(CGTACG) and d(CGATCG): implications in drug-DNA crosslink
AUTHOR(S): Gao, Yigui; Wang, Andrew H.-J.
CORPORATE SOURCE: Department Cell, Structural Biology, University Illinois Urbana-Champaign, Urbana, IL, 61801, USA
SOURCE: Journal of Biomolecular Structure & Dynamics (**1995**), 13(1), 103-18
CODEN: JBSDD6; ISSN: 0739-1102
PUBLISHER: Adenine Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Among the new generations of anthracycline drugs, morpholino-doxorubicin (MDox) and its deriv. have unusually potent activity when compared with the parent doxorubicin. 3"-Cyano-morpholino-doxorubicin (CN-MDox) has been suggested to form a covalent crosslink to DNA, although the exact mode of interactions remains unclear. To establish the structural basis of this crosslink, the authors carried out x-ray diffraction analyses of the complexes between four different morpholino-doxorubicins (i.e., MDox, CN-MDox, (R)- and (S)-2"-methoxy-morpholino-Dox (MMDox)) and two DNA hexamers CGTACG and CGATCG. Their crystal data are similar to other Dau/Dox complexes with space group P41212,a = b.apprx.28.ANG.,c.apprx.53.ANG.. The refined structures at .apprx.1.8 .ANG. resoln. revealed that two drug mols. bind to the duplex with the aglycons intercalated between the CpG steps with their N3'-morpholino-daunosamines in the minor groove. The morpholino moiety is flexible and may adopt different conformations dependent on the sequence context. The O1" atoms of the two morpholino groups in the drug-DNA complexes are in van der Waals contact. The structural results suggest possible crosslinking mechanism of CN-MDox. It is worth pointing out that by linking two piperazinyl- or piperidinyl-doxorubicins at the 1" positions a new type of bis-doxorubicin derivs. may be synthesized which may bind to a hexanucleotide sequence with some specificity.

IT **108852-90-0D**, complexes with DNA hexamers
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(crystal structures of morpholino-doxorubicin anticancer drugs complexed with DNA hexamers)

L25 ANSWER 12 OF 17 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:535813 HCAPLUS
DOCUMENT NUMBER: 122:305991
TITLE: The role of methoxymorpholino anthracycline and cyanomorpholino anthracycline in a sensitive small-cell lung-cancer cell line and its multidrug-resistant but P-glycoprotein-negative and cisplatin-resistant counterparts

AUTHOR(S): Graaf, Winette T. A. van der; Mulder, Nanno H.; Meijer, Coby; Vries, Elisabeth G. E. de
CORPORATE SOURCE: Department Internal Medicine, University Hospital, Groningen, 9713 EZ, Neth.
SOURCE: Cancer Chemotherapy and Pharmacology (**1995**), 35(4), 345-8
CODEN: CCPHDZ; ISSN: 0344-5704
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The cytotoxic action of two morpholino anthracyclines, methoxymorpholino anthracycline (MRA-MT, FCE 23762) and cyanomorpholino anthracycline (MRA-CN), was compared with the cytotoxicity of doxorubicin (DOX), the topoisomerase II inhibitor etoposide (VP-16), the topoisomerase I inhibitor camptothecin, methotrexate, and cisplatin in GLC4, a human small-cell lung-cancer cell line, in GLC4-Adr, its P-glycoprotein (Pgp)-neg., multidrug-resistant (MDR; 100-fold DOX-resistant) subline with overexpression of the MDR-assocd. protein (MRP) and a lowered topoisomerase II activity, and in GLC4-CDDP, its cisplatin-resistant subline. GLC4-Adr was about 2-fold cross-resistant for the morpholino anthracyclines and GLC4-CDDP was, relative to GLC4, more resistant for the morpholino anthracyclines than for DOX. Overall, MRA-CN was about 2.5-fold more cytotoxic than MRA-MT. The cytotoxicity profile of the morpholino anthracyclines in these cell lines mimicked that of camptothecin.

IT **108852-90-0**, FCE 23762
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(toxicity of methoxymorpholino and cyanomorpholino anthracyclines in a sensitive human small-cell lung-cancer cell line and its multidrug-resistant and cisplatin-resistant counterparts)

L25 ANSWER 13 OF 17 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:474506 HCAPLUS
DOCUMENT NUMBER: 122:255325
TITLE: Stretching HPLC sensitivity to measure subnanogram levels of FCE 23762, a novel anthracycline, and its 13-dihydro metabolite in human plasma
AUTHOR(S): Breda, M.; Pianezzola, E.; Benedetti, M. Strolin
CORPORATE SOURCE: Department Pharmacokinetics and Metabolism, PHARMACIA Farmitalia Carlo Erba, Milan, Italy
SOURCE: Methodological Surveys in Bioanalysis of Drugs (**1994**), 23(Biofluid and Tissue Analysis for Drugs, Including Hypolipidaemics), 263-8
CODEN: MSBDE6; ISSN: 1464-3421
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A HPLC method for detg. FCE 23762 and its metabolite in plasma was developed and validated down to 0.5 ng/mL concn.
IT **108852-90-0**, FCE 23762
RL: ANT (Analyte); **THU (Therapeutic use)**; ANST (Analytical study); BIOL (Biological study); USES (Uses)
(stretching HPLC sensitivity to measure subnanogram levels of FCE 23762 anthracycline and its 13-dihydro metabolite in human plasma)

L25 ANSWER 14 OF 17 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:279633 HCAPLUS
DOCUMENT NUMBER: 122:71371
TITLE: Synthesis and study of structure-activity relationships of new classes of anthracyclines

AUTHOR(S): Suarato, Antonino; Angelucci, Francesco; Bargiotti, Alberto; Caruso, Michele; Faiardi, Daniela; Capolongo, Laura; Geroni, Cristina; Ripamonti, Marina; Grandi, Maria
CORPORATE SOURCE: R&D Oncology-Immunology, Pharmacia-Farmitalia Carlo Erba, Milan, 20159, Italy
SOURCE: ACS Symposium Series (**1995**), 574(Anthracycline Antibiotics), 142-55
CODEN: ACSMC8; ISSN: 0097-6156
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Structure-activity studies in the field of anthracyclines have been very fruitful in defining those moieties that are necessary to produce derivs. active on MDR tumor cells. The authors have found that substitutions on the sugar part of anthracyclines are fundamental to confer activity on MDR cells in vitro. In particular, compds. substituted at C-3' of the sugar moiety with 4-morpholino group or selected potential alkylating moieties are able to overcome resistance both in vitro and in vivo.

IT **160398-83-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(structure-activity relationships of new classes of anthracyclines as neoplasm inhibitors)

L25 ANSWER 15 OF 17 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:22322 HCAPLUS
DOCUMENT NUMBER: 122:177802
TITLE: Functional studies with a full-length P-glycoprotein cDNA encoded by the hamster pgp1 gene
AUTHOR(S): Devine, Scott E.; Melera, Peter W.
CORPORATE SOURCE: Mol. and Cell Biol. Grad. Program, Univ. Md. Sch. Med., Baltimore, MD, 21201, USA
SOURCE: Cancer Chemotherapy and Pharmacology (**1994**), 33(6), 465-71
CODEN: CCPHDZ; ISSN: 0344-5704
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Hamster cells grown in culture may, like human and mouse cells, develop multidrug resistance (MDR) when exposed to certain cytotoxic chemotherapeutic agents. Several phenotypic features that are characteristic of MDR have been described; these include (1) resistance to many structurally and functionally unrelated drugs that have different cellular targets and modes of action; (2) reversal of MDR by certain agents, including verapamil and cyclosporin A; and (3) reduced intracellular drug accumulation relative to that of drug-sensitive cells. In this report we show that the introduction and overexpression of the hamster pgp1 cDNA confers to otherwise drug-sensitive cells an MDR phenotype with these features. Moreover, pgp1 transfectants showed varying degrees of resistance to anthracycline analogs, indicating that structural analogs of commonly used anticancer agents are capable of circumventing drug resistance conferred by pgp.

IT **108852-90-0**, DMM Dox
RL: BPR (Biological process); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(multidrug resistance to anticancer drugs as function of hamster pgp1 gene expression)

L25 ANSWER 16 OF 17 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1992:462458 HCAPLUS
DOCUMENT NUMBER: 117:62458
TITLE: In vivo antitumor activity of FCE 23762, a methoxymorpholinyl derivative of doxorubicin active on doxorubicin-resistant tumor cells
AUTHOR(S): Ripamonti, M.; Pezzoni, G.; Pesenti, E.; Pastori, A.; Farao, M.; Bargiotti, A.; Suarato, A.; Spreafico, F.; Grandi, M.
CORPORATE SOURCE: Res. Cent., Farmital. C. Erba, Nerviano, 14 20014, Italy
SOURCE: Br. J. Cancer (**1992**), 65(5), 703-7
CODEN: BJCAAI; ISSN: 0007-0920
DOCUMENT TYPE: Journal
LANGUAGE: English
AB FCE 23762 (I) is a new doxorubicin deriv. obtained by appending a methoxymorpholinyl group at position 3' of the sugar moiety. The compd. is >80 times more potent than doxorubicin, it is highly lipophilic, and presents equiv. antitumor activity when administered by i.p., i.v., or oral route. The pattern of antitumor activity of I differs from that of doxorubicin in maintaining antitumor activity against two P388 murine leukemia sublines resistant to doxorubicin and, although at borderline levels of efficacy, against LoVo human colon adenocarcinoma resistant to doxorubicin. I exhibits remarkable efficacy against MX-1 human mammary carcinoma, with most treated mice being cured both after i.v. and oral treatment. Antitumor activity was also obsd. against L1210 murine leukemia and two sublines resistant to cis-platinum and melphalan, M5076 murine reticulosarcoma, MTV murine mammary carcinoma and N592 human small cell lung cancer.
IT **108852-90-0**, FCE 23762
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antitumor activity of, in human and lab. animals tumors, resistance in relation to)

L25 ANSWER 17 OF 17 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:574058 HCAPLUS
DOCUMENT NUMBER: 115:174058
TITLE: Novel anthracycline analogs
AUTHOR(S): Grandi, Maria; Pezzoni, Gabriella; Ballinari, Dario; Capolongo, Laura; Suarato, Antonino; Bargiotti, Alberto; Faiardi, Daniela; Spreafico, Federico
CORPORATE SOURCE: Res. Dev. Oncol. Dep., Farmital. Carlo Erba Res. Cent., Nerviano, 20014, Italy
SOURCE: Cancer Treat. Rev. (**1990**), 17(2-3), 133-8
CODEN: CTREDJ; ISSN: 0305-7372
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Results presented in this report indicate that (at least with regards the exptl. models employed) classical multidrug resistance can be overcome through treatment with novel anthracyclines. An extensive in vitro evaluation has indicated that several analogs substituted in the 3' and/or 4' position of the sugar moiety are equally effective on sensitive and doxorubicin (DX)-resistant LoVo cells. Among these compds., FCE 23762, the methoxy morpholino deriv. of DX, was selected for its high in vivo antitumor activity against P388/DX murine leukemia. Other morpholino derivs. of anthracyclines, such as morpholino-DX and MX-2 have also been shown to be active against mdr-tumors. FCE 23762 is between 3- and 15-fold more potent than DX in vitro and 80 and 120-fold more potent in vivo; this latter finding indicates that the compd. is most probably

activated in vivo to a more cytotoxic metabolite still to be identified. In addn. to its clear activity on mdr cells and tumors, this novel methoxymorpholino deriv. of DX was also found to be equally or more effective than DX in exptl. solid neoplasms such as the MXI and MTV-mammary carcinomas, whereas it was less active than DX in other models such as Lewis lung carcinoma. Finally, on all tumor models tested, FCE 23762 was equally effective when given by the i.v. or oral route.

IT **108852-90-0**, FCE 23762
RL: BAC (Biological activity or effector, except adverse); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(neoplasm-inhibiting activity of, multidrug resistance antagonism in, structure in relation to, in human and lab. animal cells)

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L27 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:824131 HCAPLUS
DOCUMENT NUMBER: 134:508
TITLE: Combined method of treatment comprising an aromatase inhibitor and a further biologically active compound
INVENTOR(S): Di Salle, Enrico; Zaccheo, Tiziana; Tedeschi, Michele
PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000069467	A1	20001123	WO 2000-EP3407	20000414
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1178831	A1	20020213	EP 2000-917084	20000414
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: GB 1999-11582 A 19990518
WO 2000-EP3407 W 20000414

AB A compn. for use in breast cancer therapy in humans comprising, in amts. effective to produce a superadditive antitumor effect: (a) an antineoplastic agent in a pharmaceutically acceptable carrier and/or diluent, and (b) an aromatase inhibitor in a pharmaceutically acceptable carrier and/or diluent. The combination of exemestane and epirubicin on DMBA-induced mammary tumors in rats was more effective than either compd. alone.

IT **108852-90-0**, Nemorubicin
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antitumor agent-aromatase inhibitor combinations)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT